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ARCHIVES OF PATHOLOGY

VOLUME 13 MAY, 1932 NUMBER 5

HISTOGENESIS OF ATROPHIC CIRRHOSIS

V. H. MOON, M.D.

PHILADELPHIA

Atrophic cirrhosis will be used as a term synonymous with alcoholic, Laënnec's, nodular and portal cirrhosis. It includes a somewhat diversified group of pathologic conditions the etiology and mode of development of which have remained an enigma. Many believe that cirrhosis is essentially a chronic inflammatory process. Some authors use the term "chronic interstitial hepatitis" as covering the various forms of cirrhosis. Others discuss cirrhoses in their chapters on chronic inflammatory conditions. Such conditions have an incipience, a period of activity and progression and oftentimes a stage of latency or of healing. If a study on tuberculosis were undertaken, it should include not only the advanced, chronic and perhaps healed lesions; a study of the early, active lesions would be equally instructive. A correct conception of syphilitic disease could not be established by a study of its healed or latent effects in the tissues. By viewing only the charred ruins of a building one might fail to discover the point of origin and the cause of the fire.

Hall and Ophüls [1] found opportunity for studying active cirrhosis by selecting, from 150 necropsies on cirrhotic persons, four cases in which death resulted from other causes and in which the cirrhotic process was in a progressive stage. The subjects in these cases ranged from 28 to 48 years of age. In each of them the liver was larger than normal. Hall and Ophüls concluded that active cirrhosis has the character of a subacute proliferative inflammation with edema, leukocytic infiltration and proliferation of connective tissue, that destruction of liver cells and connective tissue proliferation occur simultaneously as the result of a common cause, and that regeneration of liver cells is a prominent feature.

Active cirrhosis has not received the close study that it merits. It has been my privilege to study material from five cases of atrophic cirrhosis occurring in children under 15 years of age, in which the process was recent and very active, and to study sixteen cases occurring

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1. Hall and Ophüls: Am. J. Path. **1**:477, 1925.

in persons between the ages of 15 and 40, in which the process was less acute. A comparison of features seen in these with those in cases occurring in the later decades of life has been instructive. The histories and postmortem observations in two of the cases have been published.[2] One of these was the case of J. S. He was one of a family of fourteen children, eight of whom were living. There was a history of scarlet fever among these children, but the parents believed that J. S. had not had it. He had never taken alcohol. An older sister had died of atrophic cirrhosis at the age of 13. Three weeks after the death of J. S., a younger brother entered Jefferson Hospital with similar manifestations. An unquestioned clinical diagnosis of cirrhosis was made. His death a few months later occurred outside the hospital. No postmortem examination was permitted. This occurrence of cirrhosis in three children in the same family has some significance.

HISTOLOGY OF ACTIVE CIRRHOSIS

The liver of this boy (J. S.) weighed 1,330 Gm.; the boy weighed less than 90 pounds (40.8 Kg.). Histologic examination showed nodules of liver cells surrounded and invaded by recently formed and actively proliferating fibrous tissue. These nodules ranged from 0.2 mm. to 10 mm. in diameter. They consisted of liver cells showing no evidence of compression or of pressure atrophy. The cells were above normal size and showed varying stages of acute degeneration. Some were swollen, and the cytoplasm was finely granular; others contained irregular clumps and masses of hyalin-appearing material that stained more densely than normal cytoplasm. This feature has been emphasized by Mallory [3] as an essential characteristic of this type of cirrhosis. Hall and Ophüls verified this feature in each of their cases. Other cells containing hyaline clumps had lost their nuclei and were in varying stages of disintegration (fig. 2). A study of this feature in many sections of active cirrhosis leads to the conclusion that it is an evidence of far advanced degeneration of the cells. If those showing it are not already necrotic, they are certainly nearing that end.

The great majority of nodules contained some cells which lacked visible nuclei and which had cytoplasm that showed irregular margins. Varying stages of cellular disintegration were evident. These were found about the margins of the nodules, or extending irregularly into them from the periphery (figs. 1 and 3). Proliferation of fibrous tissue and of capillaries from the adjacent stroma appeared where disintegration of liver cells was evident. It was seen adjacent to cells

2. Moon, V. H.: Am. J. M. Sc. **177**:681, 1929.

3. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914, p. 505.

showing advanced degeneration. It was not seen among or adjacent to liver cells that were nearly normal. Numerous nodules were present showing all stages of destruction of liver cells and fibrous tissue replacement. Figure 3 shows a nodule with destruction of liver cells and fibrous tissue replacement about the periphery. Figure 4 shows nodules in which only a few liver cells remain, and figure 5 shows an area from which all liver cells have disappeared and in which they have been replaced by newly formed scar tissue containing many bile ducts. It should be emphasized that such areas do not show the connective

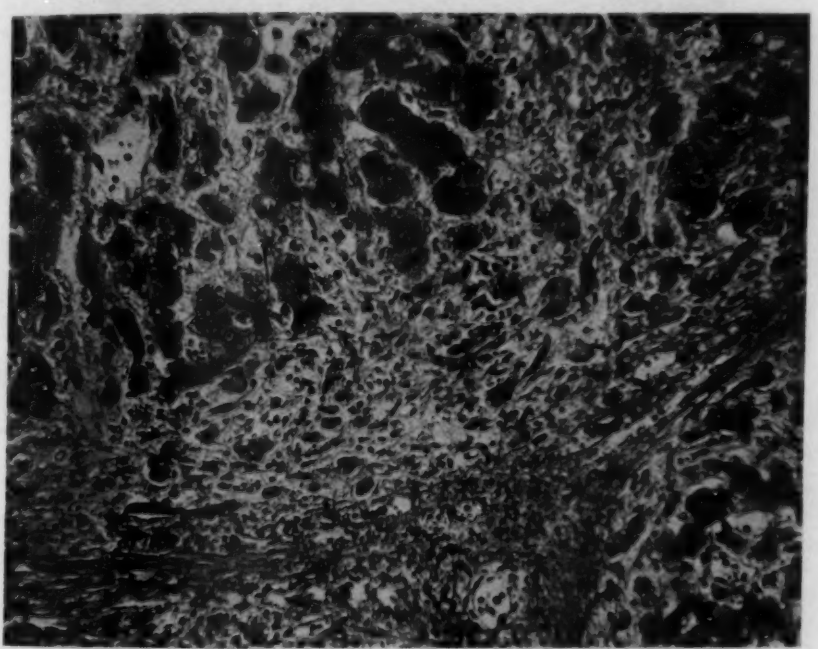

Fig. 1.—Active cirrhosis, the margin of a nodule. Degeneration and disintegration of liver cells and inflammatory infiltration and proliferation of fibrous tissue are shown; × 200.

tissue cells and fibrils lying parallel in strands. That feature appears to be produced by compression. As liver cells in uninjured groups proliferate actively they produce an expanding nodule that compresses the soft, newly formed stroma into a parallel position as shown in figure 6. Later these bands may contract causing atrophy of the enclosed liver cells, as seen in later stages of cirrhosis. Such a process explains the development of globular nodules with bands of connective tissue extending concentrically about them, which is the characteristic architecture of Laënnec's cirrhosis.

There has been discussion as to the sequence of events leading to the perinodular fibrosis. Ghon [4] and other European pathologists maintained that the fibrosis precedes the degeneration and destruction of liver cells. Some believe that the destruction of liver cells occurs first, and that the fibrosis follows. Still others, avoiding controversy in the absence of definite evidence, suggest that the two processes occur simultaneously. The latter statement is true as pertaining to the liver in general or to representative sections of it. Destruction of liver cells is seen; proliferation of connective tissue is seen; they occur simul-

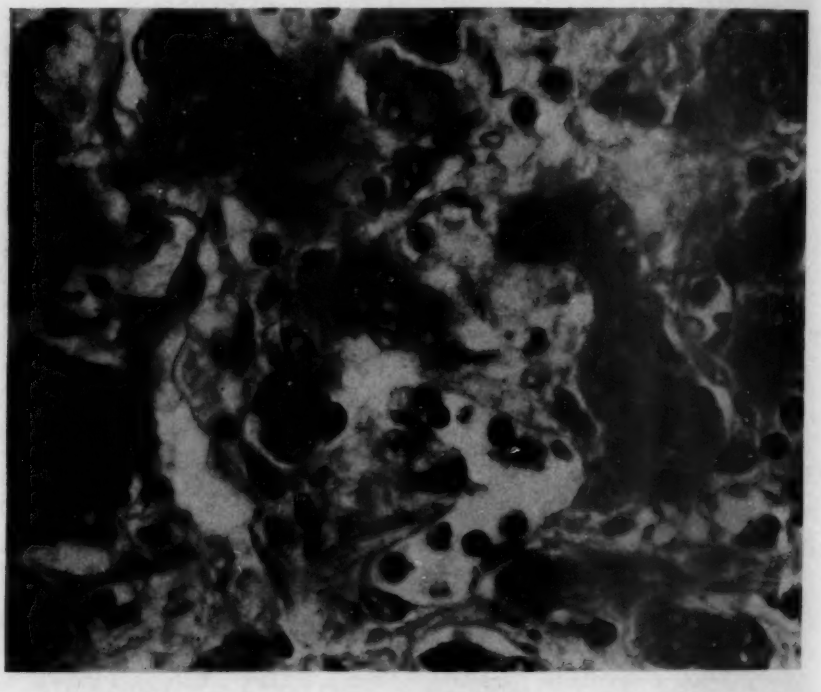

Fig. 2.—Active cirrhosis, an area near the margin of a nodule. Heavy, lumpy masses, hyaline in character, are seen in liver cells. Edema, débris of cells, polymorphonuclear and mononuclear cells are present. A few fibers of newly formed connective tissue are shown; × 800.

taneously in that sense. But observations of such areas show that the cells are undergoing destruction and cytolysis just a little beyond the margin of connective tissue proliferation (fig. 1). This observation may be verified an infinite number of times in sections from active cirrhosis. I have not seen instances in which the connective tissue

4. Ghon, A., in Aschoff, L.: Pathologic Anatomy, ed. 7, Jena, Gustav Fischer, 1928, vol. 2, p. 886.

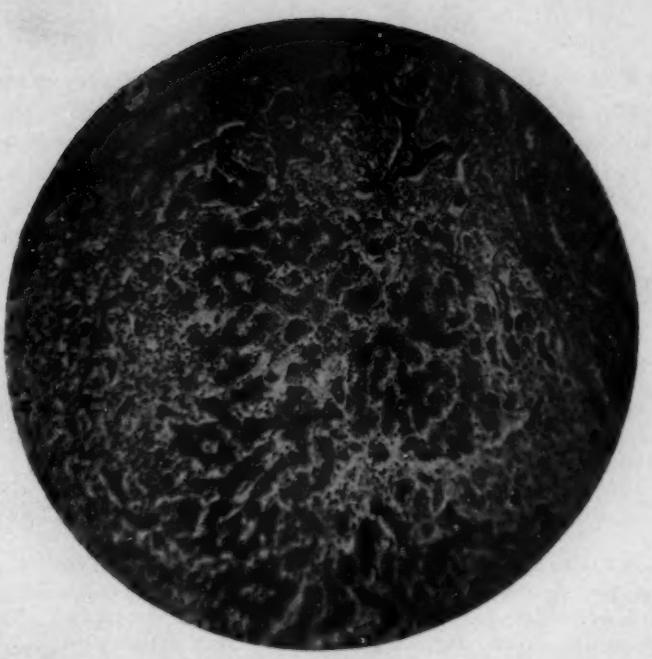

Fig. 3.—Active cirrhosis, small nodule, the margins of which are undergoing destruction and replacement. Numerous bile ducts are seen; some are atypical and resemble syncytial masses; × 100.

Fig. 4.—A nodule in which destruction and replacement are more advanced than in figure 3; × 100.

Fig. 5.—A nodule from which all liver cells have disappeared. This is soft granulation tissue containing many bile ducts. Such fibrous tissue is easily compressed into a band of parallel fibers by the expansive growth of an adjacent hyperplastic nodule; × 100.

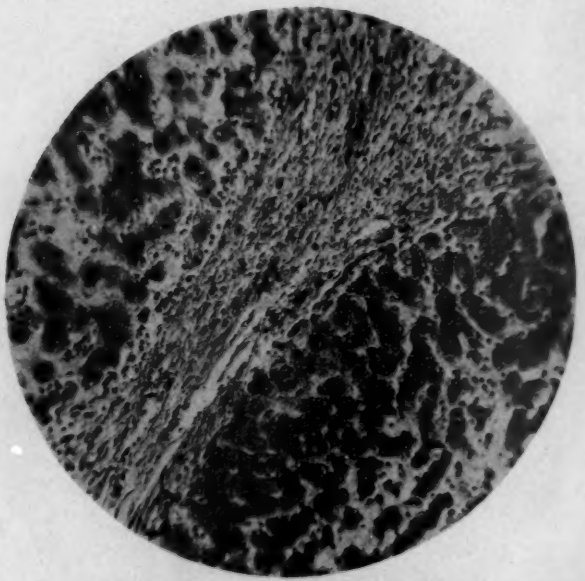

Fig. 6.—Hyperplasia of uninjured groups of cells produces expanding nodules, which compress the soft fibrous tissue into bands. These nodules are presently destroyed by action of the injurious agent. Degeneration is beginning in the nodule at the left. Later it would resemble that shown in figure 3; × 100.

proliferation was not perceptibly behind the degeneration and destruction of liver cells. The process is similar to that in other instances of progressive inflammation. Destruction of parenchymatous tissue occurs first, and replacement with fibrous tissue follows.

Other observers have made a similar interpretation. MacCallum [5] gave a concise description of the process:

> The liver-cells are killed in patches—whole lobules and groups of lobules at a time, or only parts of lobules. There remain irregular masses of liver tissue partly disconnected from their bile ducts. . . . The masses of liver-cells quickly increase in size by multiplication of their cells, new capillaries are formed in every direction, and this labyrinth of cells expands, pressing the stroma away on all sides. For a time the liver-cells are normal, but then comes another injury, and many of the hyperplastic nodules are partly destroyed. The whole process is repeated, and not only once, but many times. It is clear that this must lead to an extraordinary distortion of the liver's structure. There are no longer lobules, but only nodules produced by the hyperplasia of smaller groups of cells which were left intact.

This is directly contrary to the supposition that the cirrhotic process is primarily one of fibrous tissue proliferation, and that reduction of liver parenchyma results from the contraction of the fibrous tissue. Studies of sections from active cirrhosis reveal no evidence to support such a supposition. They tend to support MacCallum's conception.

The proliferation of bile ducts is a prominent feature in active cirrhosis. Many bile ducts appear normal in structure. Others (fig. 3) are atypical and resemble syncytial masses irregular in form and having no lumen nor even a tubular arrangement. Not all authors are agreed that actual proliferation of bile ducts occurs. Some believe that the apparent increase is merely relative; that, with the disappearance of liver lobules, the bile ducts located at their periphery are brought closely together. The numerous bile ducts seen in figures 4 and 5 do not support such a supposition. These ducts lie in all planes, and their long axes extend in every direction. Many cross each other at various angles. Such positions would not be produced by compression of liver substance resulting from destruction of lobules. An actual count was made of the bile ducts seen in sections of normal and cirrhotic livers. A section of normal liver 1 cm. square and 5 microns thick, contained from 340 to 470 visible bile ducts. A similar area of cirrhotic liver contained from 4,790 to 6,640 bile ducts. The cirrhotic liver contained about fourteen times as many bile ducts per gram as were found in normal liver. The cirrhotic liver was larger than normal for a subject of similar body weight. Proliferation of bile ducts seems the only adequate explanation for such an actual increase.

The cellular infiltration in areas of active destruction of liver cells and new tissue growth consisted almost entirely of polymorphonuclear

5. MacCallum, W. G.: Text-Book of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 304.

cells. A few monocytes and lymphocytes were present. No abscesses or areas of dense inflammatory infiltration were seen in any part of the liver. The infiltration within the bands of fibrous tissue showed a higher percentage of lymphocytes than was seen in areas of active inflammation.

Studies on each of three other cases of cirrhosis occurring in children showed no essential differences from the features seen in the case of J. S. There were minor variations in the acuteness and extent of injury, but the same salient features were exemplified in each of the four actively cirrhotic livers.

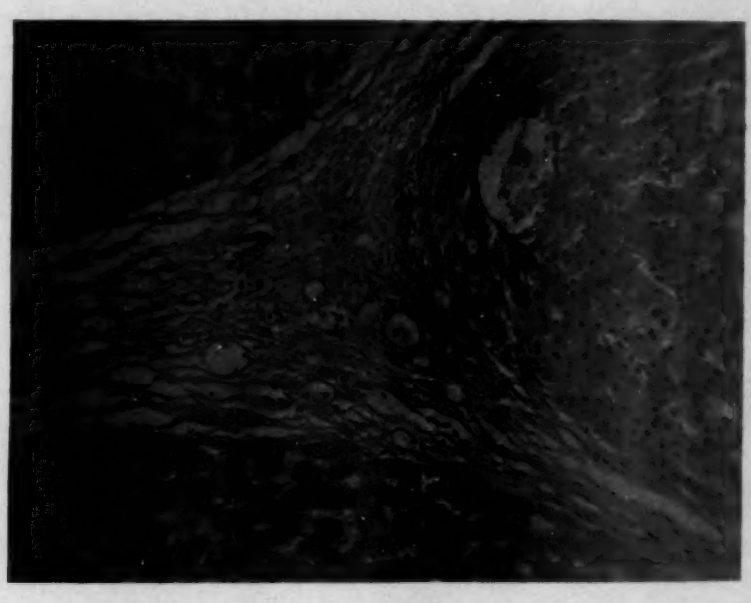

Fig. 7.—Healed cirrhosis from a child, 9 years old. There is no degeneration of liver cells or inflammatory reaction. The bands consist of mature fibrous tissue, none of which is in process of formation. No organisms were found in this liver; × 200.

The fifth case was that of a child 5 years of age in which enlargement of the liver and spleen with progressive anemia was followed by splenectomy with recovery. Four years later the child died of a malignant tumor associated with giant follicular lymphoid hyperplasia. Postmortem examination showed marked atrophic cirrhosis in addition to the malignant tumor.[6] The histologic features presented a sharp contrast to the active process seen in the four cases described. Large

6. Dr. B. S. Kline, Mount Sinai Hospital, Cleveland, provided me with the clinical and postmortem data in this case and gave me an opportunity to compare sections from it and from an additional case with those in the other cases studied.

nodules of liver cells were enclosed by dense bands of connective tissue, which was mature (fig. 7). The fibers were typically elongated and lay parallel in compact strands which contained vessels and bile ducts that appeared normal. The liver cells showed no evidence of degeneration and destruction. There were no hyaline masses in the cytoplasm, no leukocytic infiltration and no recent proliferation of connective tissue. The lobular architecture of the liver was distorted somewhat, but the cells lay in strands as normally. The lobular veins were eccentrically located.

This was a case of healed cirrhosis occurring in childhood following splenectomy. Removal of the spleen may have removed an important causative factor before irreparable damage was done to the liver. This supposition is in keeping with surgical experience. Splenectomy in early stages of cirrhosis may interrupt the process, and recovery may follow.

HISTOLOGY OF LESS ACTIVE CIRRHOSIS

Atrophic cirrhosis occurring in children is more acute and active than that seen in adults. Cirrhosis occurring in early adult life usually shows histologic evidence of greater activity than that seen in later decades of life. The clinical manifestations show a corresponding variation. The course is more rapid, and the physiologic disturbances are more acute in the earlier than in the later periods. Each of the four cases of active cirrhosis seen in children ended fatally within a year from the onset of the disease. The case of J. S. ran its complete course in ten weeks. The cases occurring before the age of 40 usually run their course in from one to three years. Cases developing after the age of 40 are usually more chronic and may last for from two to ten years. These generalizations, drawn from a review of clinical histories, admit exceptions. The insidious beginning of cirrhosis, especially in adults, makes impossible any precise statements concerning the duration of the disease.

The histology of cirrhotic livers in young adults shows the same characteristics of a productive inflammatory process as those in children. There are progressive degeneration and necrosis of liver cells. The degenerated cells contain irregular masses of hyalin-appearing substance. There is evidence of progressive destruction of groups of liver cells and replacement with fibrous tissue (fig. 8). Fibroblasts and recently formed fibrous tissue are seen in such areas. The bands that characteristically enclose islands of liver cells are more dense and apparently consist of more mature fibrous tissue than that seen in active childhood cirrhosis.

The character of the cellular infiltration varies widely. Polymorphonuclear cells are numerous about the areas where liver cells show

degeneration and necrosis and where proliferation of fibrous tissue is active. Lymphocytic and plasma cell infiltration is more prominent in adult than in juvenile cirrhosis, and the process shows other evidences of greater chronicity. The cirrhotic process is active, but the rate of progress appears to be slower.

CIRRHOSIS WITH FATTY CHANGES

Frequently fatty changes of varying degree are associated with cirrhosis. These have been interpreted variously. Many European pathologists classify fatty cirrhosis separately. Most English and

Fig. 8.—Moderately active cirrhosis in a man, aged 54. The bands consist of mature fibrous tissue. Active destruction of liver cells, inflammation and connective tissue proliferation are seen, but not so extensively as in very active cirrhosis. No organisms were found in this liver; × 200.

American writers discuss it as a variation of atrophic cirrhosis. The cases of juvenile cirrhosis studied showed no associated fatty changes. Such changes were found frequently in adults. The degree of fatty change varied exceedingly. In most cases, some cells were found containing visible fat globules. In perhaps 30 per cent of the cases of adult cirrhosis there was a rather marked amount of fatty change, and in a few the fatty changes were so marked as to dominate the histologic picture. In such livers, the characteristic features of active cirrhosis were not different from those already described (fig. 9). There was

evidence of progressive degeneration and destruction of liver cells. Many contained irregular masses of hyaline matter. Cellular infiltration and proliferation of fibrous tissue were prominent. The injury or combination of injuries that causes cirrhosis may be expected to affect fatty livers as readily as those containing no fat. Fat may accumulate more readily in a damaged liver than in a normal one. The progressive degenerative changes occurring in the cells as a part of active cirrhosis may include varying degrees of fatty degeneration and infiltration. This would be more likely to occur in the more slowly progressing cases. Fatty changes are seen frequently in chronic cirrhoses occurring

Fig. 9.—Very active cirrhosis in a fatty liver; marked degeneration and destruction of liver cells; active inflammation and proliferation. Hemolytic streptococci were cultivated from this liver; × 400.

in adults, especially in those addicted to alcohol. They are not seen in the rapidly progressing cirrhosis of childhood.

There seems to be no justification for a separate classification of cirrhosis on the basis of fatty changes.

LATENT OR HEALED CIRRHOSIS

Frequently postmortem examination reveals a typically cirrhotic liver in a case that gave no clinical evidence of that condition. McCartney [7]

7. McCartney, J. S., Jr.: Abstr., Am. J. Path. **7**:572, 1931.

reported a clinical and pathologic study of 297 cases of cirrhosis. He stated that about two thirds of these were clinical and one third latent. In a comparison of sections, particularly from patients of advanced age, one sees marked variation in the activity of the cirrhosis. In some cases there is evidence as described, of progressive cirrhosis. In others such evidence is slight or is entirely absent. No progressive degeneration of liver cells is seen. There are no hyaline masses in the cytoplasm. There is no polymorphonuclear infiltration. Connective tissue proliferation is slight. The dense bands of fibrous tissue that surround nodules of liver cells may contain a few or many lympho-

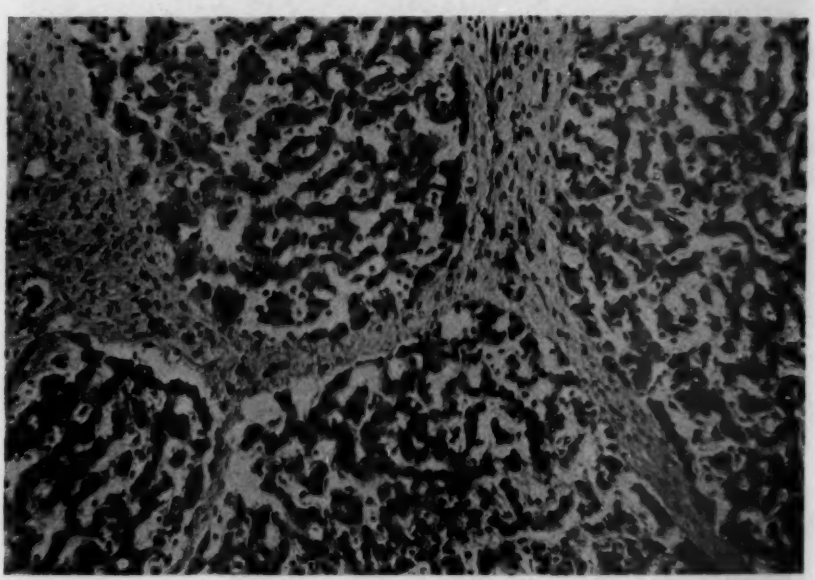

Fig. 10.—Healed cirrhosis in a man, aged 67, who showed no clinical evidence of cirrhosis. Death occurred from pneumonia. There is no degeneration of liver cells, inflammatory reaction or recent growth of fibrous tissue. No organisms were found in this liver; × 150.

cytes, but it is mature, adult fibrous tissue. Many of the liver cells may contain pigment, and they may be irregular in size and shape as if showing atrophy from pressure. In some cases, the liver cells may even be arranged in strands with well defined sinusoids between them (figs. 7 and 10).

I reviewed the stained sections from forty-four recent postmortem examinations on adults in which atrophic cirrhosis was found. Without reference to the clinical histories, these were classified as to the activity of the process. In every instance in which histologic evidence of activity was slight or was absent, reference to the clinical history

showed that there had been no ascites, no tendency to bleed, no splenic enlargement nor other signs of cirrhosis, and a clinical diagnosis of cirrhosis had not been made. There were instances, however, in cases not recognized clinically as cirrhosis, in which there was histologic evidence of activity. The activity in these cases was less marked than in the cases recognized clinically as cirrhosis.

The histologic evidence indicates that cirrhosis is the result of a progressive inflammatory process having a proliferative rather than an exudative character. This process is seen in its most active form in cases occurring in children. The inflammatory process presents more evidence of chronicity in young adults, and still more such evidence in the later decades of life. There are histologic evidences of healing or of latency of this chronic inflammatory process. Such evidences are seen most frequently in subjects over 50 years of age.

Mallory laid stress on the hyaline masses seen in the cytoplasm of the liver cells. He regarded them as characteristic and diagnostic of this type of cirrhosis, for which he uses the term alcoholic, although he does not claim that alcohol is anything more than a contributory cause. I have found these hyaline masses in each case of active cirrhosis regardless of the age of the subject. They are numerous in the very active cirrhoses of childhood. They are less numerous in sections from less active cirrhosis, and I have not found them in latent or healed cirrhosis. I regard them as evidence of the activity of the process, and their number as one of the indexes of activity, rather than as a diagnostic feature for atrophic cirrhosis as a type.

A pathologic condition of the spleen was a regular feature in all the cases of active cirrhosis that I have seen. The character and significance of this will be discussed in a later communication.

The active inflammatory character of progressive cirrhosis suggests infection as a probable cause. It is difficult to produce such a process by the use of intoxicating agents alone. Opie [8] produced cirrhosis experimentally by a combination of intoxicating agents and infection. Forms of cirrhosis have been produced by infectious agents alone. Attention was called recently [2] to infection as a cause of juvenile cirrhosis. In that article, observations and experiments of others were cited supporting the supposition that infection may be an important etiologic factor. The case of J. S., referred to in the present article, was one of those in which streptococci were cultivated from the liver as reported.

Since the publication of that paper I and my associates, F. W. Konzelmann and H. L. Stewart, have cultivated hemolytic streptococci from the livers in five cases of active cirrhosis. Details of these cases

8. Opie, E. L.: J. Exper. Med. **12**:367, 1910.

and of experiments based on them will be reported later. Frequently bacteria may be found in large numbers in sections from active cirrhosis appropriately stained. Paraffin sections of liver preserved by Zenker's method are suitable. Sections should be 5 microns or less in thickness and should be stained either by Gram's technic or by the Gram-Weigert modification. The areas of degenerated liver cells in the nodules of active cirrhosis usually contain a few cocci. Frequently these are present in large numbers. Their grouping is irregular. They occur in pairs, in short chains of six or eight, and in irregular clumps. They may be seen in disintegrating or in degenerating liver cells and in the intercellular spaces. A few are seen within leukocytes. Phagocytosis is not marked in such tissues. They are rarely seen in the areas of connective tissue proliferation. They are found in largest numbers in the very active cirrhosis of childhood and in smaller numbers in early adult cirrhosis. I have found them only occasionally, and then in small numbers, in moderately active cirrhosis in adults. I have not found any bacterial forms in the latent or healed stages of cirrhosis.

MacMahon and Mallory [9] reviewed the literature on streptococcus hepatitis, and reported five cases in four of which they demonstrated streptococci in the livers. The fifth they regarded as a healed streptococcal lesion. Two of the cases had the features of acute degeneration and necrosis of liver cells and an inflammatory and reparative response resembling that which I have described as occurring in active cirrhosis. These might possibly be cases of cirrhosis in an incipient stage. A third case was one in which a section of liver, excised during cholecystotomy, was normal histologically. Subsequently chills and fever developed, later jaundice appeared and finally ascites, which was tapped on two occasions. The liver at this time was definitely enlarged. The patient's condition progressed, and eight and one-half months after the operation he died with extensive cirrhosis of the liver. The authors' histologic description corresponds to that which I have given for active cirrhosis. Numerous streptococci were seen in sections of the liver. They regarded it as a chronic lesion due to streptococci of moderate virulence causing widespread gradual necrosis with fibrous tissue proliferation. They suggested a possible relationship between streptococcus infection and both acute yellow atrophy and cirrhosis, but refrained from drawing unwarranted conclusions.

Mallory [10] and Adami [11] reported the finding of bacilli in cirrhotic livers. Thus far I have found only coccal organisms. Hall and Ophüls [1] examined sections, stained by Giemsa's method, from four cases of

9. MacMahon, H. E., and Mallory, F. B.: Am. J. Path. **7**:299, 1931.
10. Mallory, F. B.: Bull. Johns Hopkins Hosp. **22**:69, 1911.
11. Adami, J. G.: Lancet **2**:396, 1898.

active cirrhosis, but saw no bacterial forms. I have had little success in demonstrating bacteria in tissues by Giemsa's method. Perhaps my technic was imperfect, or perhaps that method is less effective than Gram's method.

Cocci were found in large numbers in sections from four cases of juvenile cirrhosis (fig. 11). They were found in smaller numbers in nine cases of cirrhosis in adults. No cocci were found in the liver of the child whose cirrhotic process was interrupted by splenectomy, nor in any case of latent or healed cirrhosis in adults.

Studies of sections of active cirrhosis have made inescapable the conclusion that it is a progressive inflammatory process. Such processes are most frequently the result of infection. The infectious character of

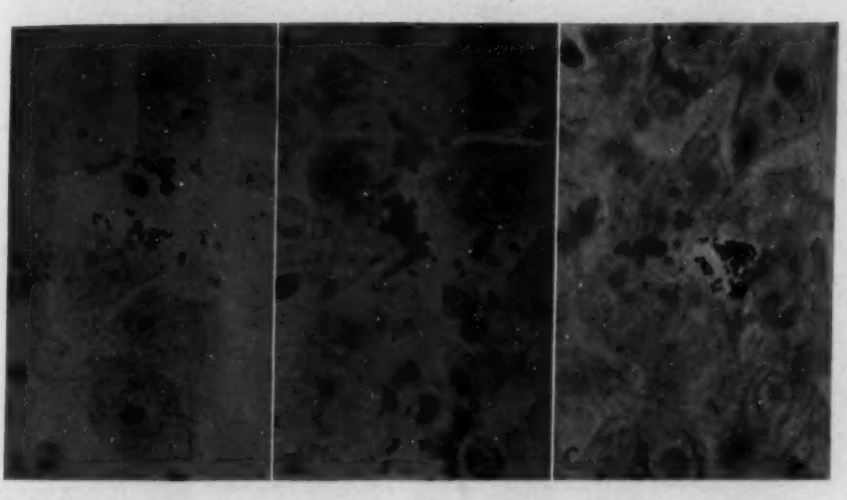

Fig. 11.—Sections from three cases of very active cirrhosis seen in children. Hemolytic streptococci were cultivated from the livers A and B. No cultures were made from C. Cocci are most numerous in the débris of disintegrated liver cells. A few are seen in other liver cells and within phagocytes. Zenker fixation; paraffin sections; Gram stain; × 1,500.

cirrhosis has been suggested by many previous observations. In view of these, the frequent demonstration of organisms in cirrhotic livers is of interest. The finding of cocci in such livers should be as significant as the finding of spirochetes in cases in which a syphilitic origin was suspected.

CONCLUSIONS

Atrophic cirrhosis is the result of a progressive inflammatory process, proliferative rather than exudative.

This process shows variation in activity and may be seen in latent or healed stages. The most active process is seen in juvenile cases. The latent stages are seen most often in adult life.

The acuteness or latency of the process frequently parallels the clinical manifestations.

There is evidence, in active cirrhosis, that degeneration and destruction of liver cells precedes the replacement by connective tissue.

No morphologic reason is found for placing cirrhosis with fatty changes in a separate class.

Cocci may be demonstrated frequently in sections of active cirrhosis. This observation lends support to the supposition that infection is an important etiologic factor.

EFFECT OF DIACETONE ALCOHOL ON THE LIVER OF THE RAT

HADDOW M. KEITH, M.B. (Tor.)
ROCHESTER, MINN.

In a study in rabbits of experimentally produced convulsions and their prevention [1] it was noted that of the four derivatives of acetone tested, diacetone alcohol had the most marked anticonvulsive effect. This is of particular interest in relation to the effect of ketogenesis on epileptic attacks. Although the explanation of the action of the ketogenic diet is not yet clear, it has been shown that certain of the acetone bodies in themselves have a definite anticonvulsive effect. Before attempting to use diacetone alcohol therapeutically it was necessary to determine its toxic effect. Walton, Kehr and Loevenhart [2] had shown that the maximal tolerated intravenous dose for rats was 3 cc. per kilogram of body weight. I was able to show that, when given by stomach tube, this was also the maximal tolerated dose for rabbits. A much smaller amount (0.5 cc. per kilogram of body weight) was found to be definitely anticonvulsive, with little, if any demonstrable toxic effect.

Since the liver is readily injured by toxic agents, it was determined to observe what changes might occur after a single, moderately large dose of the drug.

METHOD

Twenty adult white rats were placed in separate cages in pairs and made to fast for forty-eight hours. They were then allowed to feed for two hours, and were again made to fast for twenty-two hours. Then 2 cc. per kilogram of body weight of redistilled diacetone alcohol was administered by stomach tube. Before giving the drug, and at intervals afterward, determinations of the concentration of hemoglobin in the blood (Dare) and erythrocyte counts were made. Pairs of rats were then killed at intervals of from one hour to sixty days. Sections of the liver were fixed for twenty-four hours in Zenker's solution plus a diluted solution of formaldehyde and stained with hematoxylin and eosin and with eosin azure II. Four animals were killed as controls.

Submitted for publication, Dec. 11, 1931.

From the Section on Pediatrics, the Mayo Clinic.

Work done in the Division of Experimental Surgery and Pathology, the Mayo Foundation.

1. Keith, H. M.: Proc. Staff Meet., Mayo Clin. **5**:204, 1930; **6**:410, 1931; Am. J. Dis. Child. **41**:532, 1931; J. Pharmacol. & Exper. Therap., to be published.

2. J. Pharmacol. & Exper. Therap. **33**:175, 1928.

OBSERVATIONS

As evidenced in the accompanying table, there was destruction of erythrocytes, with reduction of the hemoglobin content. This was present for a period of four or five days only; the values for both returned approximately to normal on the sixth day.

Microscopic examination of the liver disclosed no changes one hour after the drug had been given, but at six hours some changes appeared. There were marked activity and increase in the number of lymphocytes in the portal spaces and of the histiocytes of Kuffer cells along the vascular sinusoids; also some slight vacuolization of the hepatic cells characterized the parenchyma in the portal zones. At twelve hours,

Estimation of Hemoglobin and Erythrocytes of Rats Following One Large Dose of Diacetone Alcohol by Stomach Tube

	Before Giving Drug		After Giving Drug											
			2 Hr.		4 Hr.		24 Hr.		48 Hr.		4 Days		6 Days	
Rat	Hemoglobin *	Erythrocytes, Millions	Hemoglobin *	Erythrocytes, Millions	Hemoglobin *	Erythrocytes, Millions	Hemoglobin *	Erythrocytes, Millions	Hemoglobin *	Erythrocytes, Millions	Hemoglobin *	Erythrocytes, Millions	Hemoglobin *	Erythrocytes, Millions
1	85	5.37	..	....	..	....	..	....	..	....	..	....	..	....
2	90	5.34	..	....	..	....	..	....	..	....	..	....	..	....
3	98	5.65	90	5.30	..	....	..	....	75	4.88	..	....	..	....
4	95	5.55	90	5.38	..	....	..	....	70	4.96	..	....	..	....
5	88	5.30	..	....	..	....	..	....	76	4.84	..	....	..	....
6	90	5.40	..	....	..	....	..	....	78	4.88	..	....	..	....
7	93	5.60	..	....	..	....	78	4.75	74	4.55	..	....	85	5.22
8	95	5.85	..	....	..	....	75	4.57	70	4.40	..	....	..	....
9	90	5.35	..	....	..	....	70	4.49	66	4.31	73	4.60	80	5.18
10	85	5.32	..	....	..	....	70	4.45	65	4.24	70	4.72	80	5.10
11	90	5.33	..	....	90	5.29	..	....	..	....	..	....	..	....
12	88	5.26	..	....	90	5.30	..	....	..	....	..	....	..	....

* Per cent (Dare).

these changes were accentuated, and lymphocytic infiltration in the portal spaces had increased. Vacuolization of the cytoplasm of the hepatic cells, first evident at six hours, now involved the entire zone around the portal spaces, causing enlargement of the cells in some cases sufficient to obliterate the sinusoids. Eighteen hours after administration of the drug, vacuolization and granulation had involved from two thirds to three fourths of the lobule, but the number of lymphocytes and littoral histiocytes was even less than at the twelve hour stage.

Maximal injury was present at twenty-four hours. There was extensive cloudy swelling of the hepatic cells throughout the entire lobule, with vacuolization and granulation of the cytoplasm. This was most marked about the nuclei, although the latter were entirely uninjured. Swelling of the parenchymal cells was such as to obliterate the sinusoids completely. The histiocytes were sparse, and only a few lymphocytes could be found.

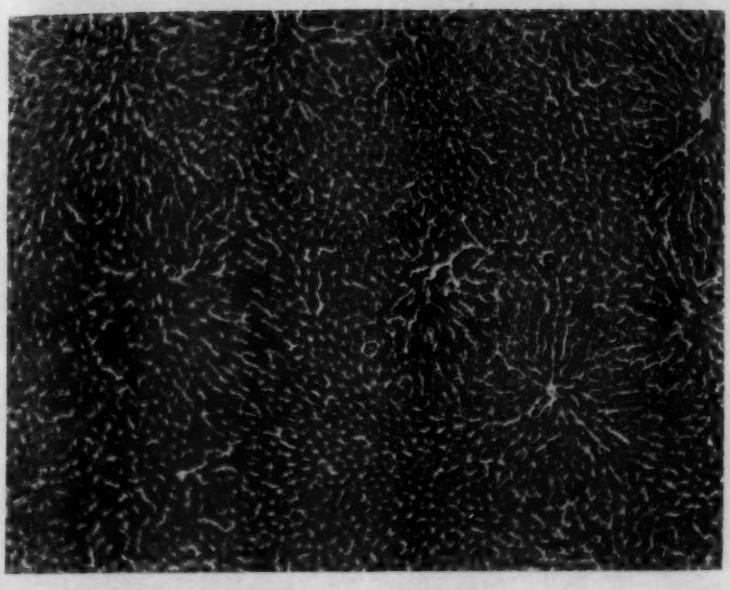

Fig. 1.—Normal liver of rat.

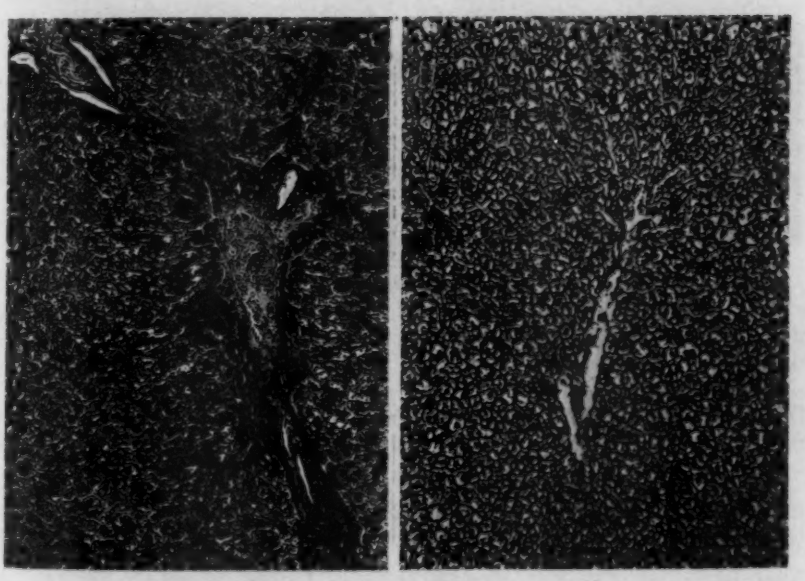

Fig. 2.—On left is shown periportal infiltration twelve hours after administration of diacetone alcohol (2 cc. per kilogram of body weight) given by stomach tube; on right, vacuolization and granulation of hepatic cells in liver of rat twenty-four hours after administration of diacetone alcohol (2 cc. per kilogram of body weight) given by stomach tube.

At forty-eight hours, beginning recovery was evident, particularly in the central portion of the lobule, from which a definite gradient of recovery toward the periphery was seen. Cells in the portal areas, however, still gave evidence of marked injury. The hepatic cells were decreased in size, and the vascular sinusoids reappeared, now containing a few erythrocytes. There was some increase in the number of histiocytes also, but this was not marked.

Recovery was well advanced at ninety-six hours, especially in the central and medial portions of the lobules. Here the cytoplasm was homogeneous, although there was some granulation still present at the

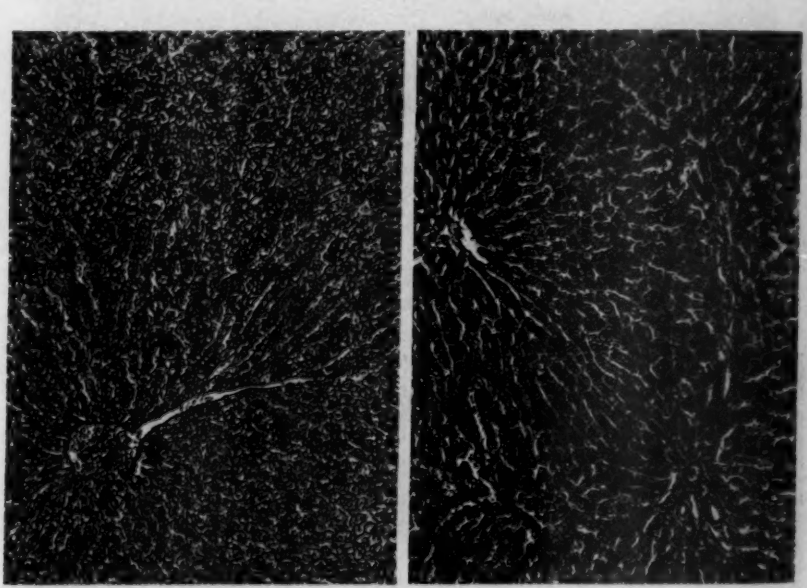

Fig. 3.—On left is shown beginning recovery of liver of rat forty-eight hours after administration of diacetone alcohol; on right, almost complete recovery of liver of rat ninety-six hours after administration of diacetone alcohol.

periphery. The sinusoids were normal throughout the lobule, but the number of histiocytes was much increased.

At seven and fourteen days, the hepatic cells were practically normal, although some granulation still persisted in the portal areas. At fourteen days, large numbers of histiocytes had appeared, and at twenty-one days these had increased to a remarkable extent.

Scattered throughout the lobules were large numbers of "nests" of these phagocytic cells, containing also nucleated erythrocytes. This presented the picture of so-called "myeloid metaplasia." The hepatic cells were, however, normal both in size and in organization. At thirty-five

days, there was no evidence of injury, and the histiocytes were again normal in number and distribution.

Two animals were killed at each interval throughout the experiment, and the changes in the two series were essentially identical. At seven days, the hepatic cells of the animal of one series had apparently recovered to a greater extent than those of the corresponding animal of the other series, and at twenty-one days there was a difference in the extent of the histiocytic reaction between the two. These, however, were only differences in degree, for the type of change was constant and readily recognizable.

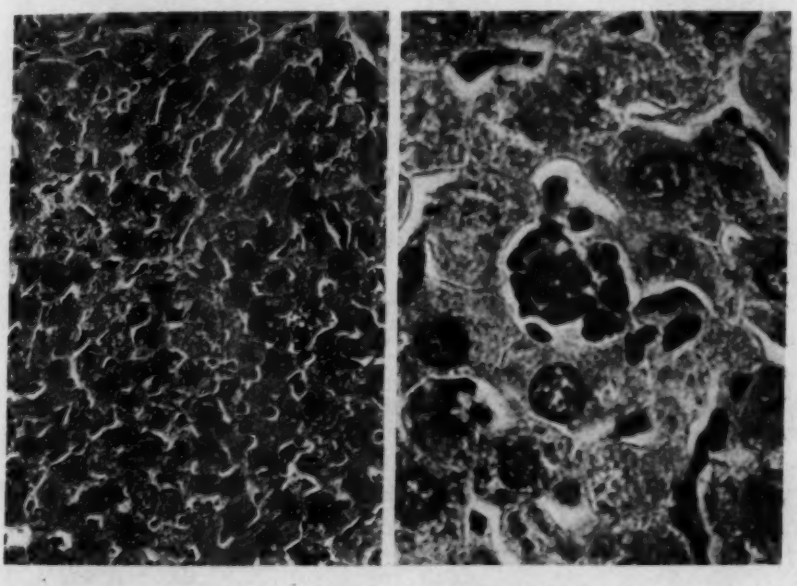

Fig. 4.—On the left are shown histiocytes in liver of rat twenty-one days after administration of diacetone alcohol; on the right, a higher magnification.

COMMENT

From the observations related, it is evident that diacetone alcohol in large quantities has two definite effects: first, destruction of erythrocytes and reduction in the amount of hemoglobin; second, injury to hepatic cells, with rapid recovery. These effects were followed by marked histiocytic proliferation. Although the amount of the drug given was fairly large, and the animals became drowsy for a few hours, they did not appear to be greatly affected otherwise. The destruction of erythrocytes was definite although not extensive, and both determinations of hemoglobin and erythrocyte counts were close to their previous values on the sixth day.

Injury to the hepatic cells commenced within six hours following injection of the drug, and reached its maximal degree at about twenty-

four hours, involving all the cells in the lobule. Recovery began within forty-eight hours, was well advanced in four days, and was practically complete in seven days. The injury to the parenchymal cell, therefore, was not severe.

The reaction of the local histiocytes in the liver is of considerable interest. Normally, these Kupffer cells, or phagocytic cells, are not abundant in the rat, but are scattered at intervals along the sinusoids, acting as scavengers and hemophages and contributing their share to the normal physiology of the organ. In the absence of the spleen, or after other destruction of the reticulo-endothelial structures, notable compensation occurs in the liver, so that these reticular cells rapidly increase in size and number, and often give rise to small foci with apparent hematopoietic capacity. The histiocytic reaction in the liver following administration of diacetone alcohol is not unlike that occurring in certain other instances of marked hyperplasia of this system. Early responses to the drug include destruction and disappearance of these cells as well as of the parenchymal cells. Subsequently, however, and coincident with repair of the lobule, new histiocytes appear from an apparently extraneous source. There is no evidence to warrant the conclusion that these vast numbers of histiocytes arise locally. Their rapid increase did not cease at the time normal parenchyma was restored, but continued well after three or four weeks had elapsed. In many instances, these proliferating histiocytes were arranged in nests of cells scattered along the sinusoids, and in some of these nucleated erythrocytes were identified. This hematopoietic activity of the reticular cells, appearing at twenty-one days after injection, and long after the erythrocyte and leukocyte counts had returned to normal, indicates, it would seem, a reaction to a persistent stimulus within the blood stream. The hemolytic action of the drug no doubt had thrown an excessive load on the normally active hematopoietic centers, such as the bone marrow; the newly formed histiocytes in the liver, reacting to the identical stimulus, may have temporarily assumed hematopoietic functions. In five weeks, the organ was entirely normal, for both parenchyma and histiocytic components had returned to a characteristic organization.

CONCLUSIONS

A single large dose of diacetone alcohol administered to rats by stomach tube causes destruction of erythrocytes and reduction in the amount of hemoglobin. Both return to normal within a few days.

There are also cloudy swelling, vacuolization and granulation of the hepatic cells, reaching the maximal degree in twenty-four hours. This process ends in complete recovery. It is accompanied by early destruction and disappearance of the histiocytes, and is followed by late reappearance of these cells in vastly increased numbers with hematopoietic activity.

MULTIPLE GANGLIONEUROMA

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The term "ganglioneuroma" has been applied to different kinds of tumors occurring either in the central or in the peripheral nervous system in which ganglion cells have been found. Just as in the spongioblastomas one may find all transitions from the most primitive spongioblast to adult fibrillary astrocytes, so in the ganglioneuromas one may find transitions from primitive neuroblasts to adult ganglion cells. In many ganglioneuromas occurring in the brain, admixture with neoblastic glial elements may be found. A comprehensive review of this subject was given by Wahl.[1] More recently a collection of ninety-three reports of cases from the literature was published by McFarland.[2] They gave evidence of the various locations in the body where such tumors occur. The present case is added because it seems to represent the only example, as far as we can determine, in which ganglioneuromas of benign type were found simultaneously in the cervical and abdominal regions, one in the region of the stellate ganglion, the others retroperitoneally.

A white woman, 23 years of age, was admitted to Passavant Hospital in the service of Dr. A. H. Curtis. Her complaints dated back over a period of one and one-half years. During this time she had lost 25 pounds (11.3 Kg.) in weight, had felt excessive fatigue and had noticed bilateral pressure in the inguinal region similar to menstrual pain. At the age of 4 years, she had had a lump removed from the left side of her neck, which was said to have been a "fatty nerve tumor." One month after its removal it reappeared and had been present until four weeks before, when it had been removed by Dr. Geza de Takats. It was situated deep in the anterior region of the neck, in the vicinity of the stellate ganglion. It was of the size of a child's fist and extended from the edge of the pleura to the transverse process of the fourth cervical vertebra.

Vaginal examination by Dr. Curtis revealed a small, freely movable uterus, displaced to the left, and an ill defined, relatively fixed, sarcoma-like mass, located

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From the Department of Surgery and the Institute of Neurology, Northwestern University Medical School.

1. Wahl, H. R.: J. M. Research **30**:205, 1914.
2. McFarland, J.: Arch. Path. **11**:118, 1931.

retroperitoneally in the right pelvis, which faded away as it entered the mid-abdomen. At operation, a chain of tumor masses, four or five in all, was found retroperitoneally to the right of the spine, extending from the kidney down into the pelvis. These masses were rubbery or gummatous in their consistency, relatively fixed, and apparently moderately vascular, and did not contain softened areas. The left kidney was about one-half normal size, and the left adrenal gland, which was from 3 to 4 times normal size, contained cystic areas.

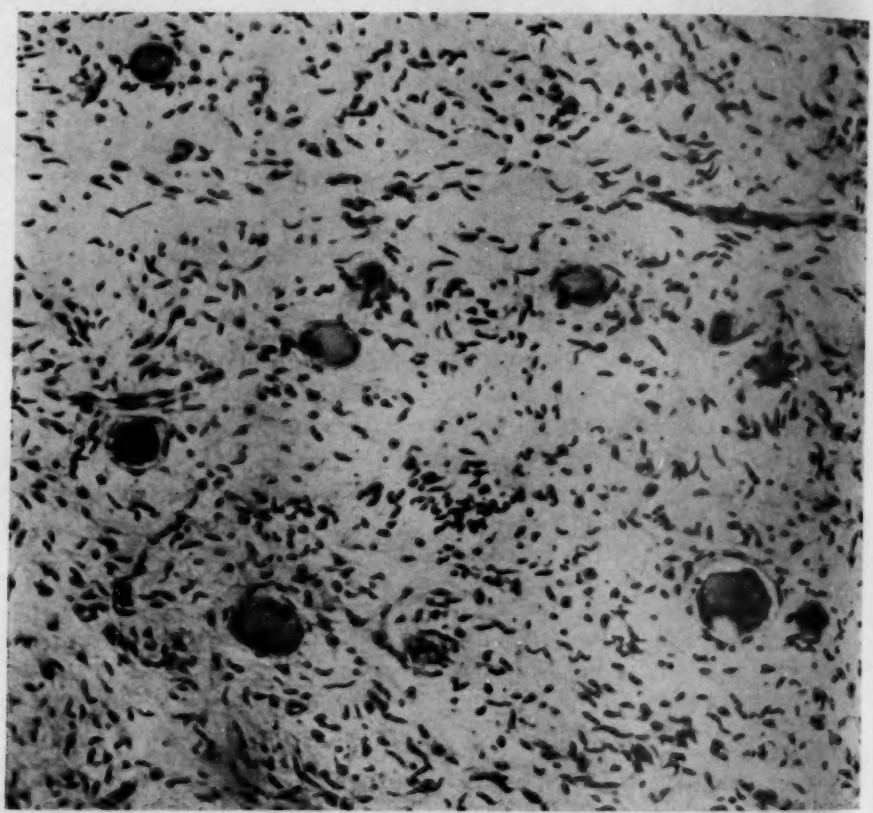

Fig. 1.—Section stained with cresyl violet; Leitz objective; ocular; 10 ×. It demonstrates the general histologic appearance of the tumor. Ganglion cells of the type found in spinal ganglions are seen, with numerous spindle-shaped and oval nuclei in the rest of the tumor.

Both tumors were identical in their histologic structure. They contained ganglion cells similar to those found in spinal ganglions, which measured approximately 30 microns in diameter; each was surrounded by a fine capsule of connective tissue. They contained as a rule one, but on occasion two, large eccentric nuclei. Smaller, less well differentiated cells were infrequently seen. The main part of the tumor was formed by unmyelinated nerve fibers, which were covered

with a thin, fibrous sheath. In sections stained with cresyl violet, numerous spindle-shaped nuclei were seen, some of them assuming more oval forms. Fat tissue invaded the tumor masses, together with foci of lymphocytes.

This multiple occurrence of such an adult type of ganglioneuroma has its counterpart in the multiple neurinomas of von Recklinghausen's

Fig. 2.—Davenport stain; Zeiss objective; 3 mm. apochromatic lens; ocular, 10 ×. It demonstrates a binuclear ganglion cell with pericellular basket formation of unmyelinated nerve fibers, and unmedullated nerve fibers in the environment.

disease. It is evident from the history that a neoblastic tendency was already present in the patient in early childhood.

SUMMARY

A case of multiple ganglioneuromas is presented, with simultaneous occurrence in the neck and the retroperitoneal region.

HÜRTHLE CELL TUMOR

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AND
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Hürthle cell tumor of the thyroid gland is a proliferation of the cell described originally by Hürthle [1] in 1894 as a normal constituent of the thyroid gland, identical with the "parenchymatous" cells of Baber,[2] and as a cell capable of reproducing thyroid tissue when called on to do so. The tumor is an exceedingly rare one, only two references being found in the literature, one in Ewing's "Neoplastic Diseases" [3] (p. 953) where there is an illustration carrying the legend "Carcinoma of thyroid. Encapsulated acidophile cell adenocarcinoma. Hürthle cell tumor," and the other a recent article by Haagensen,[4] in which two cases are mentioned. The tumor may be either benign or malignant. The case we have to report is that of a benign growth, or so-called "Hürthle cell adenoma," of the thyroid gland.

REPORT OF CASE [5]

A white woman, aged 54, was admitted to Sydenham Hospital in May, 1930, in the service of Dr. Louis Friedman, complaining of swelling in the neck and fainting spells. She had had a small goiter for years, which had become appreciably larger since January, 1930, following which she had had three "spells of unconsciousness," each lasting about one hour. She was told by those who had witnessed these "spells" that there was diffuse muscular twitching during the period of unconsciousness. Since January, 1930, there had been only slight loss of weight. Palpitation of the heart followed excitement or exertion. She was not visibly nervous, and did not perspire much. The menstrual and marital histories were normal.

The lateral lobes and the isthmus of the thyroid gland were moderately and uniformly enlarged. No nodules were noted. The veins of the neck were distended. There were no ophthalmic signs of Graves' disease, and no tremors of the

Submitted for publication, Jan. 14, 1932.
From the Pathological Laboratories of Sydenham Hospital.

1. Hürthle, K.: Arch. f. d. ges. Physiol. **56**:1, 1894.
2. Baber, E. C.: Phil. Tr. Roy. Soc., London **209**:270, 1881.
3. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, pp. 952 and 953.
4. Haagensen, C. D.: Am. J. Cancer **15**:2063, 1931.
5. Dr. Louis Friedman and Dr. William Stone placed this case at our disposal.

fingers. There was slight enlargement of the heart to the left and downward, with a blowing systolic murmur at the apex. There was marked pulsation of the abdominal aorta.

The basal metabolic rate (Sanborn-Benedict machine under optimal conditions) on May 8 was + 40. With rest and compound solution of iodine, it was reduced by May 13 to + 18. On May 15, under local anesthesia, three quarters of the right lobe of the thyroid gland was removed. The patient was discharged on May 24.

Ten months later the patient returned complaining of a peculiar sense of constriction about the head. There was marked enlargement of the thyroid gland from the left lobe past the midline. The swelling was solid, not tender, and firmly attached to the trachea. There were no subjective symptoms or physical signs of Graves' disease. The basal metabolic rate, however, was + 41. On March 4, 1931, the left lobe was removed. Subsequently the basal rate dropped to + 3, and when the patient was seen in July, it had dropped to — 18. At that time, a large nodule was palpated at the site of the second operation, but this later disappeared.

Microscopic examination of the right lobe of the thyroid gland revealed a toxic, nonexophthalmic goiter. In the left lobe, microscopic section showed the tumor to consist of many small alveoli, long strands of palisade-like cells and, occasionally, syncytium-like masses. Some alveoli contained a small amount of colloid. The cells were large, fat-free cells, either polyhedral or irregularly shaped. They were clearly outlined. The cytoplasm was oxyphilic and finely granular. The nuclei were eccentrically placed and were small and vesicular, with nucleoli, and were rich in chromatin. No mitotic figures were seen, though a few double nuclei were noted. In addition, the picture of toxic, nonexophthalmic goiter was present, with many areas of lymphocytic infiltration. The diagnosis was "toxic nonexophthalmic goiter, and Hürthle cell adenoma of the thyroid gland." When the original slide was studied again, the same changes were recognized, in addition to the former picture (figs. 1 and 2).

The rarity of the growth and the apparent lack of literature concerning it have led us to seek more information, and to attempt to determine the exact nature of the tumor.

The Hürthle cell is a large, eosinophilic cell, rich in cytoplasm, found by Hürthle [1] on the outer surfaces of the walls of the follicles of the thyroid gland. He, as well as Zielinska,[5a] who had also seen these cells, believed them to be masses of immature cells concerned in the growth of the follicles. However, Mueller [6] and Michaud,[7] in describing the thyroid gland histologically, failed to find these cells, and Mueller stated that they were probably parts of the wall of the follicle cut obliquely. Maximow [8] also proved by careful dissection of normal and pathologic thyroid glands, and with wax-plate reconstructions, that these interfollicular cells do not exist. Boechat,[9] in his thesis on the thyroid gland, failed to mention any cells resembling these

5a. Zielinska, M.: Virchows Arch. f. path. Anat. **136**:170, 1894.

6. Mueller, L. R.: Beitr. z. path. Anat. u. z. allg. Path. **19**:127, 1896.

7. Michaud, L.: Virchows Arch. f. path. Anat. **191**:63, 1908.

8. Maximow, A.: Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1930, p. 704.

9. Boechat, P. A.: Thèse, Paris, 1873, p. 12.

follicular cells. Horsley,[10] in investigating the embryonic tissue seen by Baber and by Hürthle in the thyroid gland, stated that in some animals a large quantity of this tissue could be found in a single mass beneath the capsule of the thyroid gland, but separately and distinctly encapsulated. He believed that the researches tended to refute the like-

Fig. 1.—Hürthle cell adenoma under low power magnification.

lihood of this tissue ever developing into acini of the thyroid gland. Our conclusion from these facts is that the Hürthle cell is not always present in the parenchyma of the thyroid gland, though it sometimes may be, and that it therefore is not an integral part of that gland.

10. Horsley, V.: Lancet **2**:1163, 1886.

Welsh [11] in 1898, describing the parathyroid glands, referred to the masses of embryonic tissue seen in the thyroid gland by Hürthle and by Zielinska, and stated that they correspond sometimes to the internal, and sometimes to the external parathyroid glands. Erdheim [12] also referred to oxyphilic cells in the parathyroid glands that resembled the Hürthle cells. Sandstroem,[13] who was the first to describe the parathyroid glands, also thought that they had an embryonic function and would

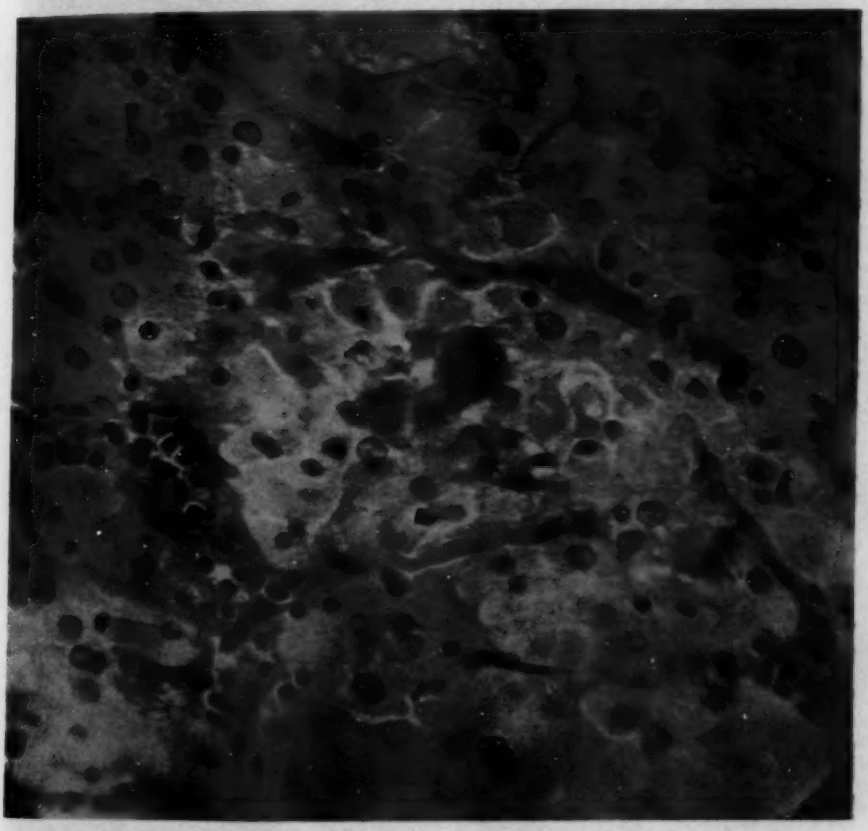

Fig. 2.—The same tumor as shown in figure 1, but under high power magnification. Note the large, polyhedral cells, "foamy" and granular, with nuclei placed eccentrically. Some are rich in chromatin, with many nucleoli. Some colloid-filled acini are seen. Note the resemblance to adrenal gland cells and hepatic cells.

form fresh thyroid tissue when required. The cells of the internal parathyroid glands described by Kohn [14] were obviously the same cells

11. Welsh, D. A.: J. Anat. & Physiol. **32**:292, 1898.
12. Erdheim, J.: Beitr. z. path. Anat. u. z. allg. Path. **33**:158, 1903.
13. Sandstroem, I.: Schmidt's Jahrb. **5**:423, 1880.
14. Kohn, A.: Arch. f. mikr. Anat. **44**:366, 1895.

that had been previously seen by Baber, Hürthle and Zielinska and thought by them to be interfollicular cells with an embryonic function.

The Hürthle cell therefore appears to be identical with the oxyphilic cell of Welsh, which is one of the two types of cells making up the parenchyma of the parathyroid gland. These cells have been described by Welsh [15] as being of two types, namely, chief (principal) cells and oxyphilic cells.

The former have a relatively small, clear cytoplasmic body with a relatively large, clear nucleus. The latter have a large, usually granular cytoplasmic body with a small, dark nucleus. The granules are highly oxyphilic. Later evidence tends to show that these two types of cells are identical, but represent different stages of activity, the oxyphilic cells showing the resting stage, and the principal cells the discharging stage. Erdheim [16] believed that these are all chief cells up to the tenth year, and Harnett [17] concurred in this opinion, because such cells do not begin to secrete until a person has reached the age of 10.

That these cells of the parathyroid glands should be found within the parenchyma of the thyroid gland is not surprising when one considers the anatomic and embryologic relationships of the two glands. A well known case of such ectopia is that of the presence of suprarenal gland rests in the kidney (Grawitz [18]). This similarity has already been noted by Berard and Alamartine.[19] Also there is the case reported by Kolodny [20] as one of hypernephroma of the thyroid gland, though he was unable to locate a primary tumor. This case Hendriock [21] considered as an example of a tumor of the thyroid gland definitely arising from a parathyroid gland rest.[22]

The parathyroid glands are by no means constant in their anatomic position. Most frequently there are four glands, the superior pair being situated near the lateral margin, and the inferior pair near the

15. Welsh, D. A.: J. Path. & Bact. **5**:201, 1898.

16. Erdheim, J.: Wien. klin. Wchnschr. **41**:974, 1901.

17. Harnett, W. L.: A Histological Study of the Human Parathyroid Gland, 1907, Longmans, Greene & Co., London.

18. Grawitz, P.: Virchows Arch. f. path. Anat. **93**:39, 1883.

19. Berard, L., and Alamartine, H.: Compt. rend. Soc. de biol. **66**:619, 1909.

20. Kolodny, A.: Arch. Path. **1**:37, 1926.

21. Hendriock: Centralbl. f. allg. Path. u. path. Anat. **38**:385, 1926.

22. The resemblance of parathyroid gland cells to suprarenal gland cells has been noted before (Richardson, quoted by Geis: Ann. Surg. **47**:523, 1908), and they have also been found to resemble the carotid body cells (Prenant: Cellule **10**:18, 1894) and the hypophyseal cells (Welsh, footnote 15). This close resemblance between chromaffin cells in different glands has been further established by Koopman (Frankfurt. Ztschr. f. Path. **25**:342, 1921), who bases this resemblance on the acidophilia of the cells. The analogous occurrence of ectopic tumors of these glands may be more than just a coincidence.

median margin, of the lateral lobes of the thyroid gland. However, aberrant parathyroid glands are common (Marine [23]). They may be found on the anterior surface of the thyroid gland (Millzner [24]), at

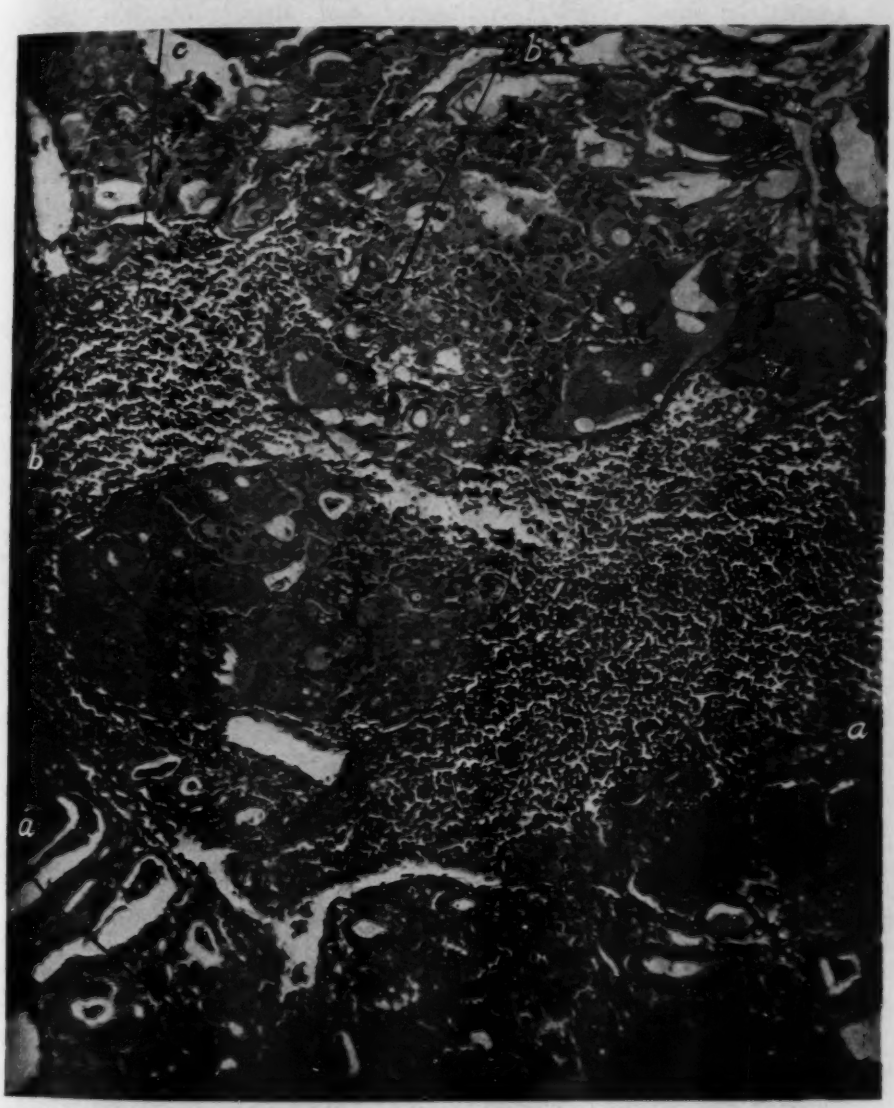

Fig. 3.—Thyroid gland with parathyroid gland inclusions: (*a*) acini of thyroid gland; (*b*) parathyroid gland (Hürthle) cells; (*c*) diffuse lymphocytic infiltration.

23. Marine, D., in Tice, Frederick: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 8, p. 264.

24. Millzner, R. J.: J. A. M. A. **88**:1053, 1927.

the base of the tongue (Wood[25]), at the base of the thymus (Duperie,[26] Pepere[27]), in the hypophysis (Pepere[27]), within the thorax (Meyer[28]), and in the thyroid gland (Sandstroem,[13] Kohn,[14] Cristiani,[29] Gley,[30] Getzowa,[31] Welsh,[11] Wellbrock[32] and others). According to Wellbrock,[32] careful search in removed thyroid glands has shown eight per cent of them to contain aberrant parathyroid gland tissue. We have recently seen such a case (fig. 3).

The apparent cause of these so frequent aberrant positions of the glands lies in their embryologic relationships. The parathyroid glands develop from thickenings of the third and fourth branchial clefts on each side. The primordium on the third cleft is close to the bud of the thymus, while that on the fourth cleft is close to the lateral bud of the thyroid gland (Maximow[33]). A pair of diverticula arise from the fifth branchial pouch and form what are termed the ultimobranchial or postbranchial bodies (Getzowa[31]). These fuse with the thyroid gland, but contribute no true thyroid gland tissue (Gray[34]).

From the anatomic, histologic and embryologic data just recorded it is readily seen why parathyroid gland rests of oxyphilic cells occur within the thyroid gland, and also that the Hürthle cell is, in all probability, the oxyphilic or Welsh cell.

The fact that these inclusions of parathyroid gland cells can assume neoplastic characteristics is also established. True tumors of the parathyroid gland, however, are not common, most of the new growths being in reality hyperplasias associated with rickets, osteitis fibrosa, osteoporosis, nephritis, epilepsy and other conditions (Goedel,[35] Erdheim,[36] Kerl,[37] Gold,[38] Mandl,[39] MacCallum,[40] Wilder,[41] Thompson and

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25. Wood, F. C.: Proc. New York Path. Soc. **16**:84, 1916.
26. Duperie, R.: Compt. rend. Soc. de biol. **99**:324, 1928.
27. Pepere, A.: Arch. de méd. expér. et d'anat. path. **20**:21, 1908.
28. Meyer, A. W.: Anat. Rec. **3**:272, 1909.
29. Cristiani, H.: Arch. de physiol. norm. et path. **5**:279, 1893; J. de physiol. et de path. gén. **7**:261, 1905.
30. Gley, E. A.: Arch. physiol. norm. et path. **24**:81, 1892; Compt. rend. Soc. de biol. **4**:18 and 46, 1897; Compt. rend. XII Cong. Internat. Med., Moscow **3**: 190, 1897; Presse méd. **6**:17, 1898.
31. Getzowa, S.: Virchows Arch. f. path. Anat. **188**:181, 1907.
32. Wellbrock, W. L. A.: J. A. M. A. **92**:1821, 1929.
33. Maximow (footnote 8, p. 700).
34. Gray, H.: Anatomy, Philadelphia, Lea & Febiger, 1924, p. 1282.
35. Goedel, A.: Wien. klin. Wchnschr. **38**:246, 1925.
36. Erdheim, J.: Ztschr. f. Heilk. **25**:1, 1904.
37. Kerl, W.: Deutsche med. Wchnschr. **21**:127, 1925.
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Harris,[42] Hunter,[43] Herxheimer,[44] Schmorl,[45] Todyo [46] and Parreiro and Casto Freire [47]). These changes may be primary, leading to the conditions mentioned (Mandl [48]), or they may be secondary to those conditions (Boyd, Milgram and Stearns [49]).

As is well known, true tumors of the parathyroid gland can be either benign or malignant. These tumors have been found both external to and within the thyroid gland.

The parathyroid gland tumors within the thyroid gland were described by Langhans,[50] who classified the epithelial tumors of the thyroid gland as follows: (1) proliferating struma, (2) carcinomatous struma, (3) metastasizing struma, (4) parastruma (parathyroid or glycogen-containing struma of Kocher), (5) small alveolar, large cell struma (probably struma postbranchialis of Getzowa), (6) papilloma and (7) cancroid.

In describing the fifth group, Langhans stated that the cells of the alveoli of the struma can be compared with hepatic cells or fat-free cells of the adrenal glands. The cells are very large, from 15 to 30 microns in diameter, polyhedral and rich in cytoplasm, which is acidophilic. They contain no lipoids. The nucleus is often eccentric, measures from 6 to 8 microns in diameter, and is round and vesicular, with its membrane folded and wrinkled; it contains numerous chromatin granules and threads, with a small eosin-red nucleolus.

When Getzowa [51] described struma postbranchialis, she classified the cells into four types: (1) water-clear cells, (2) rose-red cells, (3) oxyphilic cells of Welsh and (4) syncytium-like cells.

The tumor corresponding to the small alveolar, large cell struma of Langhans and to the oxyphilic cell tumor of Getzowa is the tumor seen by us. It is described by Ewing [3] as consisting of "relatively small, well-formed alveoli lined by one or more layers of very irregular cells. Some are clear, cuboidal or cylindrical, or irregularly polyhedral. Others are large, sometimes of giant size, finely granular, eosinophile and opaque, resembling granular suprarenal or liver-cells. The nuclei are small, vesicular, with visible nucleoli." Having seen two such tumors, Ewing suggested that these oxyphilic cells may represent hypertrophic Hürthle cells, and thus called the growth Hürthle cell tumor.

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CONCLUSIONS

The Hürthle cell, as an integral part of the thyroid gland, does not exist, because it is not always present in the gland, it is identical with the parathyroid gland oxyphilic cells of Welsh, and it takes its embryologic origin in close relationship with the parathyroid gland.

Hürthle cell tumor of the thyroid gland is a misnomer because it leads to the erroneous impression that it originates from the tissue of the thyroid gland.

The tumor really originates from parathyroid gland rests within the thyroid gland, and is an example of parastruma as described by Langhans and by Getzowa; in its relationship to the thyroid gland, it corresponds to renal hypernephroma.

The symptoms of convulsions and constriction exhibited by our patient suggest increased secretion of the parathyroid glands.

RADIATE FORMATION DUE TO A HYPHOMYCETE (ASPERGILLUS?)

AS SEEN IN PULMONARY GRANULOMATOSIS OF A CAPYBARA (HYDROCHOERUS HYDROCHOERUS); THE NATURE OF FUNGUS INCRUSTMENTS IN GENERAL

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That a moisture-loving and aerobic plant like a mold should be found parasitic in the lungs of such an animal as the capybara can occasion no surprise to the sophisticated pathologist; however, he may still be curious as to the rôle of the fungus as a pathogen and the part that the animal might play as a porter of analogous human fungous disease. But in addition to these considerations, which belong in the field of comparative pathology, three sidelights have developed that have immediate bearing either on human medicine or on the biology of fungus: (1) the formation of radiate fungi in disease other than actinomycosis; (2) a new, unique morphology for radiate fungi (except in experimental rabbits); (3) the nature (genesis) of the hyaloid incrustations [1] occasionally observed on other pathogenic fungus cells, such as Coccidioides immitis and Actinomyces bovis. This feature of incrustation, indeed, is, in the final analysis, the determining factor for the radiate fungus effect both in this capybara and in true actinomycosis; hence it merits special attention in its essentially mycologic and biologic aspects. The incrustation on the fungus of the capybara was particularly welcome for study in this connection because it affected a cell intermediate in size between the taxonomically widely separated fungi, Coccidioides and Actinomyces, constituting a stepping-stone that makes it simpler to compare the biologic processes concerned in the formation for all three, as well as for others.

HISTORY OF CASE

The capybara was a full-grown female, dying Dec. 19, 1930, in captivity in the Philadelphia Zoological Garden. This animal is a rodent closely related to the

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1. This term will be employed in this paper in the loose, broad sense, i. e., simply of matter deposited on the exterior, without connoting its composition or source (internal or external).

guinea-pig (belonging to the Caviidae) and has a geographic range extending from Central to South America, i. e., from the Guianas to the river Plata in Argentina. It favors the banks of rivers and is semiaquatic in habits. During its seven months' stay in the local zoological garden, this particular animal had had no cage mates. However, its enclosure was in series with ones occupied by aquatic or semiaquatic birds (liable to and therefore potential reservoirs of aspergillosis); a small stream ran through the entire series of enclosures.

However, fungous disease was not encountered once in the fourteen capybaras on which autopsies had been done previously in the same zoological garden, and five of these had been in captivity for a longer period of time than this one (eight months, nine months, nine months, four years and eight years, respectively). The only birds upstream to the capybara had been penguins and ducks; but, significantly, a large group of the former had died more than fifteen months previously with extensive, more or less generalized aspergillosis. The ducks that were subsequently parked in the same enclosure after its disinfection, which are also liable to aspergillosis, but to a lesser degree, have not contracted aspergillosis to date. These factors of birds and Aspergillus are in point of view of da Fonseca's hints about the identity of the fungus found in the capybara. Further mention of this will be made in later paragraphs. This accumulation of evidence is thus conflicting as to the source of the infection, whether avian or related to inanimate environment, including food.

In conformity with the usual experience with wild animals, no symptoms of disease had been observed in this capybara even immediately prior to death. Dr. H. L. Ratcliffe, assistant pathologist to the garden, performed the autopsy and made the diagnosis histologically, and then referred the lungs to me for more detailed study. Since all of the tissues had been fixed in formaldehyde, cultural studies were precluded.

Necropsy.—The animal was not well nourished; fat was scanty, and the muscles were thin and pale. The skin was scaly and dry.

Internally, the outstanding finding was a perforated duodenal ulcer, with secondary serofibrinous peritonitis. The ulcer was 1 cm. in diameter and had the conventional punched-out characteristics of the lesion in man. The material around it externally was fibrinous rather than fibrous. The peritoneal cavity contained 100 cc. of bloody fluid, intermingled with flakes of pus.

There were some thin, fibrous adhesions between the cecum, duodenum and gallbladder. Except for some swelling and pallor, the kidneys appeared normal. In the spleen, the follicles were large and prominent; the pulp was bright red-brown. The lymph nodes in all regions were large, firm and pale.

The lungs, exclusively the seat of the mycotic findings in the case, were voluminous, considerably congested and edematous, and exhibited the barest suggestion of lobular consolidation, uniformly distributed through both lungs. In addition, myriads of nodules, both subpleural and interstitial, were present. The subpleural ones resembled miliary tubercles, but were perhaps paler, more translucent and homogeneous, suggesting for the moment multiple metastatic cancer. This effect was lost on the cut surface, however, where the appearance was like that of multiple, disseminated miliary tuberculosis. A predilection for peribronchial positions could not be made out. There were no cavities, sinus formations or other foci in keeping with actinomycosis of man.

Histologic Examination.—Histologic sections were cut from the following organs: heart, lungs, liver, kidney, spleen, pancreas, adrenal gland and thyroid gland. Except in the lung, no frank and significant abnormalities were recognized

in these organs. In the kidneys there was degeneration of the parenchymal cells, with thrombi in the glomerular tufts; acute degenerative nephritis was diagnosed. A moderate grade of cardiac degeneration was indicated by a dimming of transverse striations. The centers of the hepatic lobules were degenerate, and the periportal regions somewhat fibrosed. Otherwise the search for disease was without result.

Except for a few short stretches where the pleura was edematous and lightly infiltrated by lymphocytes, it could be regarded as normal. There was no excess

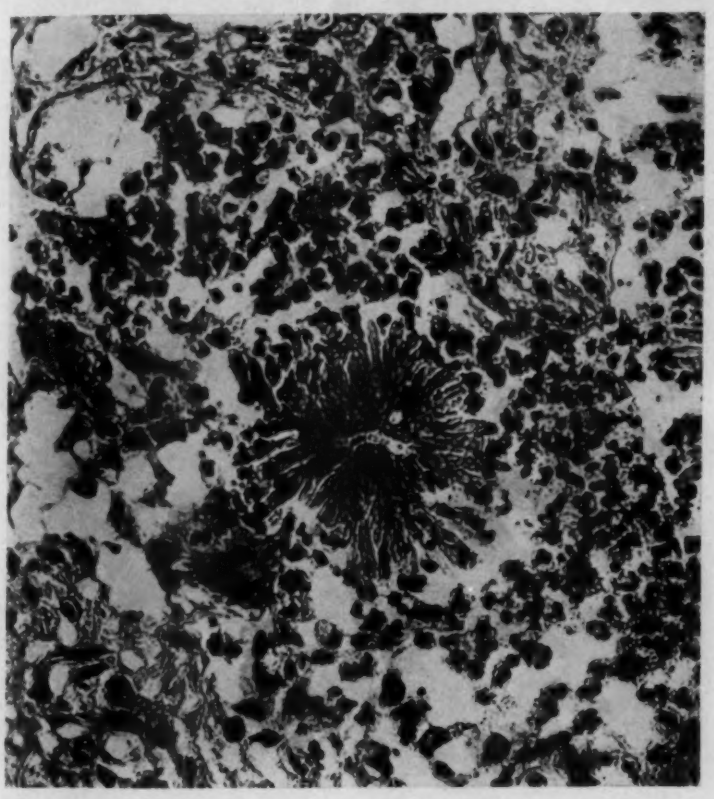

Fig. 1.—Hematoxylin and eosin preparation. A short stretch of hypha is included in the center of a radiate fungus; there is an infiltration by polymorphonuclears immediately around it, as in actinomycosis.

of fibrous tissue in the general pulmonary framework. The state of the air sacs varied widely from place to place; in but small part were they overdistended; for the most part, they appeared smaller than normal. In certain comparatively large areas, they were more or less solidly filled with a pink, finely granular precipitate of edema, red blood cells and perhaps desquamated epithelium. Fibrin, if present at all, was scanty. Phagocytes loaded with black pigment were numerous.

Granulomas: The granulomas comprised the most important feature. They were sometimes single and at other times were so closely placed as to produce comparatively large areas of consolidation. In parts, the solidifying substance was

the edema and epithelial desquamation (bronchopneumonic type of exudate) mentioned. At other times, polymorphonuclears were richly intermixed; when the latter was the case, they were generally close to the fungus organisms, which will be described later. Indeed, at times the granulomas appeared to consist almost exclusively of a group of polymorphonuclears clustered against one of these fungus organisms; however, on careful search some larger, rather granular and apparently disintegrating cells akin to endothelioid cells could generally be discerned in the periphery of the leukocytic accumulations. In larger granulomas there were increased numbers of these degenerate and more or less fused endothelioid cells.

Fig. 2.—A radiate fungus within a bronchial terminus (atrium). The iron hematoxylin preparation brings out lateral offshoots from one of the rays. The latter is not a common occurrence.

They differed from those commonly seen in tuberculosis in that whereas they had extremely broad and definite cytoplasms (often stellate in form) they were still indefinitely outlined. Indeed, the individual cells were with difficulty distinguishable from degenerate lining epithelium of the air sacs, and could, indeed, well be this. Giant cells were numerous; for the most part, they were of foreign body type. They frequently contained small portions of fungus rays. In a number of instances it was possible to make out (apparently isolated) giant cells that contained fragments of fungus, which deserve special mention because they occurred clearly within air spaces.

All of the larger bronchi were greatly distended but empty, while some of the smaller ones were completely occluded with more or less degenerated polymorphonuclears, and on search giant cells and fragments of the rays of the fungus could finally be located here also. It could be made out that there was a particular concentration of the pneumonic foci around the bronchi; but, in addition, numerous granulomas and other inflammatory effects were discoverable as far out as the subpleural parenchyma.

THE RADIATE FUNGUS

As remarked, the radiate fungus was almost invariably surrounded by more or less disintegrated polymorphonuclears. In point of size and conspicuousness, in point of radiation effect, and in point of the dense hyaloid composition of the rays, this organism was altogether comparable to Actinomyces bovis. On the other hand, the respects in which these radiate forms in the capybara differed from the conventional ones of human actinomycosis were as follows:

1. They did not exhibit the large size possible and known for actinomycosis. This could, however, be simply an expression of youth incident to the acuteness of this particular infection, the organisms not having had time to attain their fullest dimensions.

2. The organismal mass was uniformly spherical or elongated; that is, it was not lobulated as is so often the case in true actinomycosis. Again, this might be an expression of youth, but I believe that the elongated form is one to be expected—contingent on the elongated hyphae subsequently demonstrated in *in toto* preparations.

3. The radiate extensions of a mass were not club-shaped, as with actinomyces, but were more or less cylindric. However, they were of about the same length and width as those of Actinomyces bovis and were of the same hyaloid texture. The tips were not rounded conformable to their being part of a club, but appeared broken off short; or, the tips might have a more or less definitely angular termination (gladiolar).

4. As an outstanding difference, the center of the radiating mass was not granular (more or less disintegrated fungus substance); instead the outlines of a double-contoured cell could almost always be made out. It is emphasized that this cell had only superficial resemblance to a blastomycete; it did not bud, and its outlines were not the beautiful, geometrically circular ones of a blastomycete, but were comparatively uneven as though it had felt the effect of some shrinking agent (fixative?) and had become distorted. While this asymmetry might well be regarded as a function of the size of the cell, averaging as it does well above that of Gilchrist's organism and most of the other pathogenic yeastlike forms, I doubt it, because this irregularity of form is compatible with cells that are part of the hyphal structures subsequently

demonstrated in *in toto* preparations. Furthermore, after search, elongated examples of these double-contoured structures were met, and even suggestions that they were branching.

As with Actinomyces bovis, the relationship of the external hyaloid (radiate) material to the central cell is interesting; that is, in regard to whether this material is a product of the cell or a contribution from the inflammatory processes roundabout. In any event, the hyaloid material comprising the ray extended into direct contact with the cell in the interior of the fungus. Indeed, conditions were sometimes so favorable that the substance could be observed becoming integral with the fungicellulose in the wall of the micro-organism itself. I feel very strongly that this material is fungus in production and not host tissue.

5. Yet another difference consisted in the (only occasional) presence of striations passing obliquely (laterally and centrifugally) from both sides of the axis of a given ray. This imparted a feather or herring bone appearance to the ray, as though the striations were extending out from an invisible midrib.

Gram Stain.—The gram stain was of advantage only in that portions of many, but not all, of the rays stained gram-positive (varying irregularly in color from greenish blue to purple), thus serving to identify the location of the fungus organisms more promptly during searches under low power magnification. No filamentous structures were identified, such as are seen in Actinomyces bovis, by this technic. As usual, the metachromatic granules in the interior of the central cells were gram-positive.

Giemsa Stain.[2]—Likewise, no filamentous structures were brought out by the Giemsa stain, but the outlines of the fungus organisms were sharper, as usual, than by any other staining method. The rays stained more deeply (blue) than by other stains, but their substance showed no superior or additional differentiation.

Stain for Bacteria.—As a test for the presence of Bacterium actinomycetum-comitans or other such forms, a frozen section of lung (formaldehyde-fixed) was stained in weak basic fuchsin and examined without being dried or cleared (an approach to supravital methods). No bacteria were demonstrated.

Haidenhain's Iron Hematoxylin.—This regressive method stained the hyaloid substance of the rays of the fungus black. As usual, it was particularly useful for bringing out details, such as the plane of junction between the radiate extensions and the wall of the cell. The wall of the cell took the red counterstain. Again, the hyaloid incrustation was found to come into most intimate contact with the wall of the cell.

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2. Including the May-Grünwald modification.

However, the two did not blend; at least, in some cases the wall of the cell was recognizable as a pink, double-contoured shell independent of the rays.

Polarized Light.—None of the fungus was anisotropic in sections; this also applies to the spinulous processes on the rays.

Fungus in in Toto Preparations.—In order to examine further the branching of the fungus, which could not be satisfactorily determined in paraffin sections, and to get an idea of the form of the fungus *in toto*, pulmonary substance containing granulomas was softened and cleared

Fig. 3.—Mycelium in the center of a radiate fungus from pulmonary substance leeched in potassium hydroxide solution.

by leeching in 10 per cent potassium hydroxide for several days. From time to time during this period, the material was shaken in order to facilitate softening; as the tissue had been previously fixed in formaldehyde, the pulmonary substance did not become unduly disintegrated. In the sediment of this preparation, the outlines of the rays had largely disappeared or were at most only suggested; in their stead there was a finely granular or homogeneous matrix, within which the mycelium was still splendidly preserved.

The hyphae were both simple and complex. Simpler ones consisted of a stretch of perhaps only three or four segments of fungus;

in the more complicated ones there would be three or four major branches and five or six short ones extending from the main, parent stem. The segments were broad, estimated at 4 microns in diameter, and two or three times as long. There was a definite, thick shell of fungicellulose, and in the interior a number of fine granules with two or three coarser ones. While most of the segments were cylindric, many were deformed or, what was rather striking, narrower at the proximal end than at the distal, giving a more or less trumpet shape. The terminals of some of the hyphae were bluntly bifid, recalling the form sometimes assumed by Achorion schoenleinii.

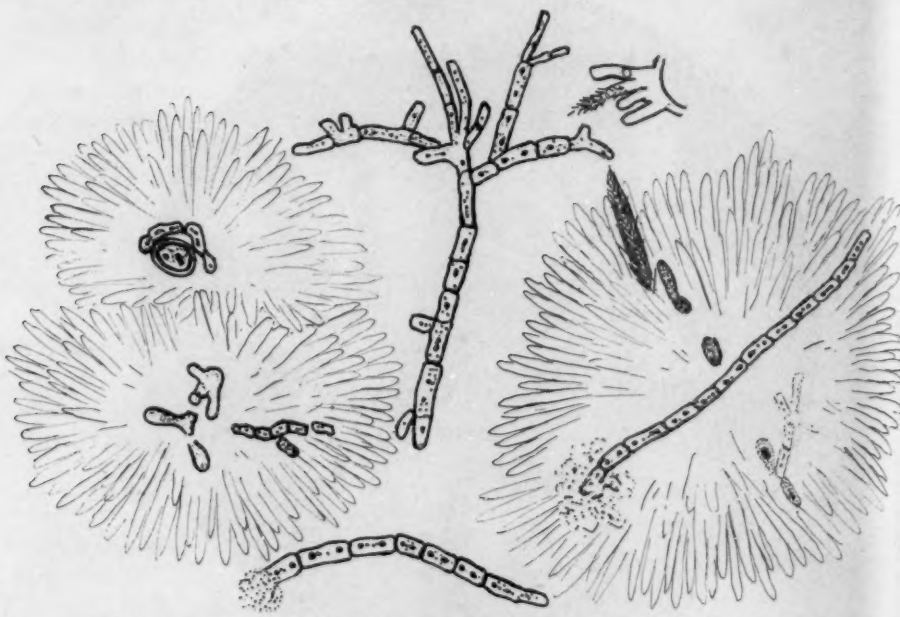

Fig. 4.—Radiate fungi leeched by means of strong alkali from pulmonary tissue. The radiations were smooth, hyaloid and faintly yellowish green. They persisted around some of the hyphae; it appears that they had been dissolved from others.

SOURCE OF THE INFECTION

The morbid anatomy (no important fibroses) seems to indicate that this infection was not far enough developed to have been contracted in the wild; the animal had been in captivity for at least seven months. My own original suspicions that the organism might be an aspergillus, contracted from waterfowl nearby, are suggestively (and independently) supported by Dr. Olympio da Fonseca:[3] "As far as my experience

3. Dr. Olympio da Fonseca, of the Oswaldo Cruz Institute in Rio de Janeiro, exchanged sections of Brazilian chromoblastomycosis for mine from the capybara.

goes," he wrote, "the thing I saw most like to that which your capybara exhibits, was obtained by intravenous inoculations of rabbits with some strains of Aspergillus fumigatus. In such cases I saw quite often, around the injected spores, club-like structures not so developed as in your capybara, but quite conspicuous. I do not think one can reach any definite conclusion in this case, as no cultures are available."

As indicated in the history of the case, all data are so circumstantial that the source of the infection must be regarded as undetermined, although the data are suggestive (avian).

IDENTITY OF THE PARASITE

The coarseness of the metachromatic granules in the interior of the cells, with at the same time the comparatively heavy and broad walls, is not unlike what is seen in Madurella, but the black pigmentation was lacking. No other specializations were discovered in this material—no chlamydospores, no arthrospores, not to say asci and other such extremely high forms. So far as the form of the fungus in this tissue is concerned, the organism could be classified no farther than as a member of the Arthrosporinae. This is not an unusual experience for even the most complicated species of fungi as they infect animal tissue; in the latter, comparatively unfavorable environment, they do not tend to produce the more highly specialized examples of reproductive bodies, but tend only to vegetate or at best to reproduce only by the formation of comparatively nondistinctive, endogenous spores known as arthrospores.

The literature on actinomycetoid forms fortunately comes to one's assistance at this point and supplies near-duplicates of the fungus of the capybara, but only in experimental [4] animals. Thus, in kidneys of rabbits, Macaigne and Nicaud [5] secured forms that appeared to be identical with it save that their radiate extensions were more genuinely club-shaped. They were remiss in descriptions of the mycelium itself, and the illustrations are poor. However, the latter are satisfying as to the general radiate form and construction of the fungus, and the spaces in the center are comparable in location and size to those of the mycelium in the capybara. If allowance is made for the larger size of the fungi studied in the rabbit (therefore probably older), it becomes easier to reconcile the difference in shape of the clubs. All things considered, I feel that the two forms may be regarded as identical

4. This is fortunate, because there is no doubt as to the identity of the causative micro-organism.

5. Macaigne, M., and Nicaud, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **52**:551, 1928.

if it is recalled how labile the morphologic aspects of the fungi are, and that an aspergillus (the French workers used a pure culture of Aspergillus fumigatus) was the etiologic factor in the capybara.

Oidium albicans, however, has to be eliminated in view of the radiate form of fungus observed in the kidney in experimental rabbits by Magrou[6] (see fig. 14). Here, again, the morphology of the mycelium in the center was not furnished in detail, but it was fully as broad as that of the capybara. The winding course described by the author may not deserve emphasis, but certainly that of the mycelium in the capybara was not winding. Furthermore, clubs were but scatteringly distributed over the exterior of this radiate form of Oidiums. All other radiate forms of fungus or "grains" (see later paragraphs) were so widely discrepant as to be readily excluded from consideration with the ones of the capybara, mainly because their centers did not exhibit *wide* mycelium. Only Madurella exhibited such mycelium, but the "grains" of the disease caused by this organism are lacking in peripheral clubs and do not enter into the problem of differential diagnosis.

Incidentally, if it can be assumed that the capybara presented aspergillosis, the survey of the literature makes it appear that this experience is unique (1) in the occurrence of radiate forms of fungus apart from experimental animals (spontaneous) and (2) in the presence of aspergillotic granulomas in the lungs. (Heretofore the pulmonary lesions have been diffuse and devoid of radiate forms. Radiate forms were found only in the kidneys.)

THE NAME OF THE DISEASE

Actinomycosis.—Certainly, this disease cannot be admitted as actinomycosis. I am not in sympathy with the policy of assigning a newly discovered disease to a previously denominated infectious disease group that has an established etiology, unless the name of the latter disease connotes also the causative organism of the new disease.[7] If, theoretically, it were possible to reconcile the fungus in the capybara with the already established genus Actinomyces, of course the name actinomycosis would be proper, but this cannot be done, because the streptothrix of Actinomyces and the broad hyphae of the fungus found in the capybara indicate widely separated taxonomic positions.

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6. Magrou, J.: Ann. Inst. Pasteur **33**:344, 1919.

7. Nicaud, for instance, while disputing "aspergillar pseudotuberculosis" as the title of the disease in his (aspergillotic) experimental animals, did so on the basis of morbid tissue discrepancies rather than differences in etiologic agent (Compt. rend. Soc. de biol. **99**:1564, 1928).

To crystallize thought, it is in order to compare the disease of the capybara and actinomycosis. First, they have in common the same fundamental reactions of the tissues. Leukocytes are massed against and directly in contact with the micro-organism, and a low grade of chronic inflammation appears immediately peripheral to this. This is a form of reaction common to a number of other infections with fungi (true actinomycosis, coccidioidal granuloma, blastomycosis). It is true that from the gross standpoint the disease of the capybara was not outstandingly suppurative. Whether it could become so in the more advanced stages cannot be predicated at present. By analogy with chromoblastomycosis, it would not be essentially suppurative, but here analogy fails one, for by analogy with actinomycosis it would be suppurative.

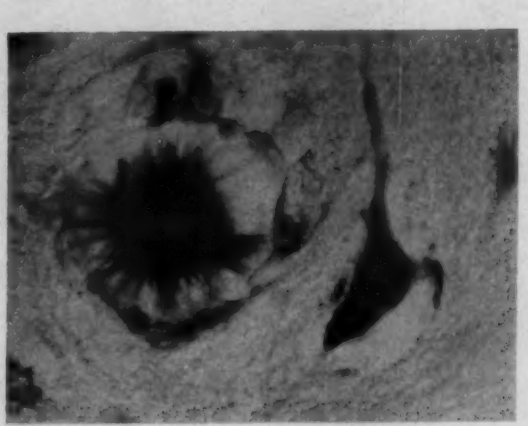

Fig. 5.—Torula histolytica in brain. Radiate extensions from the cell membrane pass outward into the thick, mucinoid envelop, bespeaking the homogeniety of the two. Dr. Walter Freeman supplied the photomicrograph.

Second, in both diseases the causative organism has the capacity to develop hyaloid incrustations that send out such processes as to impart a generally radiate form to the colony as a whole. While this is intrinsically a matter of the biology of the fungus and not of the disease process, such as should carry most weight in denominating a new disease of unknown etiology, the precedent has been already set in the case of the radiate fungus and actinomycosis. In line with the best and most conservative thought, pending more accurate determination of the identity of the fungus of the capybara, judgment is suspended as to the name of the disease.

Chromoblastomycosis.—This is introduced here because like the capybara, it is indigenous to Brazil, and its essential fungus cell is

similar to the extent of being a hyphomycete. It is caused by Acrotheca pedrosoi [8] and Phialophora verrucosa.[9] Both in culture and tissue the organisms are brownish black, whence the name "chromoblastomycosis" applied to the disease which they cause. One North American case,

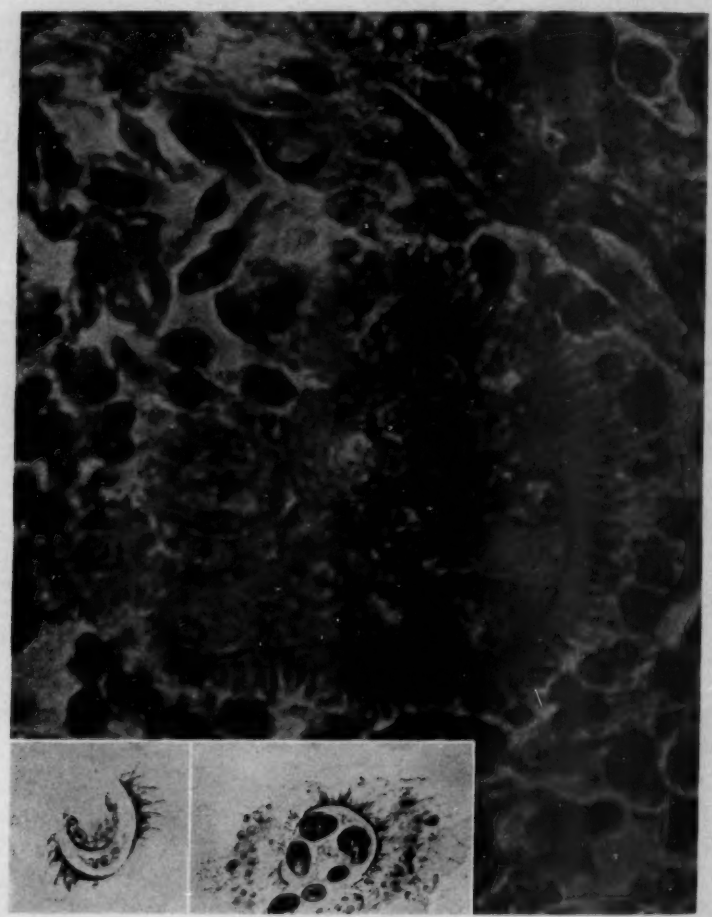

Fig. 6.—Coccidioides immitis. It shows radiate extensions from the shell of a ripe, ruptured cell containing numerous spores. The inserts are from Florence E. Ahlfeldt's paper (J. Infect. Dis. **44**:277, 1929). Dr. Ahlfeldt supplied the photomicrograph.

due to Phialophora verrucosa, has been described. Chromoblastomycosis is effectively separable from pseudo-actinomycosis, partly because the

8. da Fonseca, O., and de Area Leao, A. F.: Rev. de méd. y cir. da Brazil **38**:197, 1930.

9. Medlar, E. M.: J. M. Research **32**:507, 1915.

former is known to occur only in the skin, but particularly because radiate fungus forms have never been described for it. It will be recalled that da Fonseca exchanged sections with me and emphatically declared that they are different, to which I agree.

Aspergillosis.—Aspergillosis of man as a primary, etiologically uncomplicated process is decidedly rare; as an accompaniment of old infarcts, bronchitis and particularly tuberculosis, it is commonly found if searched for. In progress, primary, uncomplicated aspergillosis of the lungs is excessively slow—up to fifty-two years in the case of a lesion affecting, say, half a pulmonary lobe.[10] I did not find granulomas described anywhere for human lungs such as were seen in the capybara; even in experimental animals, granulomas do not appear in the lung. In man, the pulmonary lesions appear essentially as bronchiectases or as edematous necrosis; in either case, intense bronchopneumonia surrounds such lesions.

As to radiate aspergillotic forms, they appear to have been seen in man but twice. Kohn [11] reported finding in histologic sections of lungs "grains" like actinomycosis, and stated that "long slender filaments (faden) extend out from its periphery." He gave no additional information on which to base a comparison with the radiate form found in the capybara.

Boyce [12] similarly reported agglomerations in sections of the lung in which the nodule consisted almost entirely of mycelium. His illustrations depicted little if any hyaloid incrusting material; certainly, the appearances were not comparable with the radiate form in the capybara. The radiation effect in his "grains" was thus only indifferently expressed; for the most part, it was referable to the radiate arrangement of mycelium that is common to colonies of fungi in cultures. However, the terminal filaments exhibited swellings, which revives the subject of actinomycotic clubs. Unlike the latter, however, they were composed essentially of genuine, living fungus protoplasm and were not of incrustive nature.

Both as to type of tissue reaction and as to morphology of fungus, then, the aspergillosis of the capybara differed widely from that of man; indeed, were it not for the sufficiency of experimental infections in lower animals that so definitely incriminate Aspergillus, it would have been impossible to correlate the two hosts in the absence of cultures.

10. Nicaud, P.: Paris méd. **1**:163, 1928.
11. Kohn, H.: Deutsche med. Wchnschr. **50**:1332, 1893.
12. Boyce, R.: J. Path. & Bact. **1**:163, 1893.

RECONCILIATION OF ANIMAL PARASITIC AND CULTURAL FORMS

Commonly, the identification of hyphae in tissue carries the pathologist little farther than the diagnosis of mycosis; however, he is always curious as to whether similar or analogous forms are met in culture or in nature, and if so, whether they have value in identification of species. The morphologic ramifications of fungi are so manifold that the logical approach to the problem of determinative mycology in general is the other way around, i. e., through a knowledge of the habits of fungi and, after that, of the ways in which they become altered when transferred to tissue. This is seldom practical, however; mycology is almost a specialty in itself, and one that can be more reasonably dispensed with as a part of the equipment of the overloaded general pathologist. It still remains, however, that of the manifold mycobiologic phases, incrustment is a common and comparatively distinctive one ensuing when the fungus infests animal tissue; this at once commands the attention of the pathologist and justifies consideration of at least that phase.

INCRUSTMENT IN GENERAL

Taxonomic Distribution.—The bacteriologist and protozoologist are already familiar with capsule and gloae formation (Bacillus mucosus group, the staphylococci of botryomycosis, Myxosporidia). In medical mycology it is also a well known phenomenon. Not to exhaust the list, it is expressed on Saccharomyces hominis [13] and Torula histolytica [14] —in the case of the latter, both in tissue and in culture. Minor, more or less denticulate or even radiate extensions are commonly noted on Coccidioides immitis [15] and its congener, Zymonema braziliensis,[16] in tissue. Echinulate, granular projections commonly occur from the exterior of fuseaux of microsporons and other dermatophytes in culture (Sabouraud [17]).

It has probably been seen in connection with an aspergillus, as a thick membrane around terminal swelling of hyphae, in a case of Kaposi's sarcoma (Dillard and Weidman [18]). Limited as we were to histologic sections, the question arose whether the formations were expressions of calcification, i. e., deposits from host tissue outside the fungus cell, or were products from its interior. It was a simple matter

13. Castellani, A., and Chalmers, A.: Manual of Tropical Medicine, ed. 3, New York, William Wood & Company, 1920, p. 1074.
14. Freeman, W., and Weidman, F. D.: Arch. Neurol. & Psychiat. **9**:589, 1923.
15. Ahlfeldt, F. E.: J. Infect. Dis. **44**:277, 1929; Arch. Path. **2**:206, 1926.
16. Almeida, F. P.: Ann. de méd. de Sao Paulo **4**:91, 1929.
17. Sabouraud, R.: Les teignes, Paris, Masson & Cie, 1910, p. 679.
18. Dillard, J. G., and Weidman, F. D.: Arch. Dermat. & Syph. **11**:203, 1925.

to refer such formations to terminal chlamydospores, but the degree of thickening was out of proportion to anything with which we were familiar. Turning now to the botanical literature, in following through the morphologic vagaries of Aspergillus one meets the Hülle cell [19] (an abortive fruit stalk) figured by Thom and Church,[20] and on following their reference to original work by Eidam,[21a] forms similar to those in the sarcoma were found figured for Aspergillus (Sterigmatocystis) nidulans. Eidam worked with materials that were free from parasitic environment, and in his opinion the membrane was developed from the protoplasm in the interior of the cell.[21b] According to this information, membranes are capable of developing around fungus cells entirely apart from parasitic environment.

Nature and Source.—One phase of incrustment is illustrated on conidia. In culture, the granular excrescences on conidia (Scopulariopsis, Aspergillus) and on the fuseaux of various dermatophytes [17] give incrustation effects. Thom and Church,[22] in their description of the genesis of the conidium, explain such granules or other masses on the basis that they correspond to substances formed in the wall of the conidium that "give coarseness or body to the roughenings or spinulosities." This observation, of course, connotes a source within the fungus cell.

From the medical angle, interest as to the nature and source of the incrusting material has centered mainly around a second form, namely, the radiate fungus of actinomycosis. Langeron, Cauchemex and Alleaux [23] analyzed the situation in 1925. They pointed out first that there was no uniformity in the distribution, taxonomically speaking, of such matter; it appeared around bacteria (the staphylococci of botrymycosis and Actinobacillus lignieresi) as well as around filamentous forms, such as Actinomyces. Even such high forms as Monilia [6] and Sporotrichum [24] could show clubs [25]; that is, there was nothing peculiar

19. Thom agrees with Eidam; he wrote me that he believed Hülle cells to be "morphologically undeveloped stalks" (of certain reproductive structures).

20. Thom, C., and Church, M.: The Aspergilli, Baltimore, Williams & Wilkins Company, 1926, p. 21.

21. Eidam, E.: (*a*) Beitr. z. Biol. d. Pflanz. **3**:377, 1883; (*b*) ibid., p. 405.

22. Thom, C., and Church, M.: The Penicillia, Baltimore, Williams & Wilkins Company, 1930, p. 5.

23. Langeron, M.; Cauchemex, L., and Alleaux, V.: Ann. de parasitol. **3**:225, 1925.

24. Pinoy, E.: Bull. Inst. Pasteur **11**:929 and 977, 1913.

25. The original citation simply mentions Sporotrichum as a producer of clubs, without description or illustration. Subsequent authors, in repeating this citation, have given the species equal dignity with Actinobacillus as a club producer—an impression that is quite unjustified.

or specific (botanically speaking) in the formation of such matter. Incidentally, arrangement of this material in clubs or other radiate forms is likewise inconstant; with others, I have seen "grains" of Actinomyces, some of which exhibited clubs and others of which did not. In one instance, the radiate fungus exhibited clubs only at scattered points of the periphery. There are thus no rigid lines in respect to presence or absence of clubs. It still remains, however, that certain species of fungi feature clubs and rays more regularly than others; but one should always be ready and willing to recognize and accept exceptions to the rule.

The second interest of the authors just cited lay in the source and nature of the incrustment. Briefly, Pinoy's (cited by Langeron and his associates [25]) theory was that it was "a mixed formation which comes about through the digestive action exercised by the host upon the membrane of the parasite." On the other hand, Lignieres and Spitz [26] regarded it (clubs at least) as "young protoplasm, capable of budding and serving as pabulum for the filaments in the interior"; i. e., anything but expressions of degeneration or involution. The success that Bayne-Jones [27] met, confirmed by Langeron and his associates,[25] in inducing the formation of clubs in cultures appears to eliminate Pinoy's theory. It does not prove the additional contentions of Brumpt (quoted by Langeron and his associates [25]), particularly the one endowing the incrustment with vital properties. Bayne-Jones' [27] observation of filaments extending from clubs (in moist chamber) did not strengthen Brumpt's hypothesis; they sprang from filaments at the proximal end of the club rather than from the hyaloid substance of the club proper.

For Actinomyces and other slender organisms like the bacteria, I feel that the incentive for the development of the incrustations has not been proved. It is scarcely likely that Bacterium actinomycetum-comitans is the basis of the matter (having undergone lysis and coagulation), because it would have been detected long ago.

As seen in tissue, it is tempting to refer at once all of these encapsulation effects to the principles of the "Dauercyst" or resting cell so well known in protozoology; i. e., that the capsule is protective, a reaction against adversity such as may also be assumed for fungi in the comparatively anaerobic and torrid environment of mammalian tissue. However, it becomes necessary here to recall that capsule formation can appear under circumstances other than adversity. For instance, it

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26. Lignieres, J., and Spitz, J.: Bull. Soc. centr. de méd. vét. **20**:487 and 546, 1902; Rev. Soc. méd. argent. **11**:105, 1902.

27. Bayne-Jones, S.: J. Bact. **10**:569, 1925.

occurs preparatory to reproduction, as in (1) the formation of cysts among the protozoa and in (2) the formation of asci among fungi.

As to the particular aspergillotic radiate fungi described by Macaigne and Nicaud,[5] and the form isolated from the capybara, there is an explanation that I would emphasize in an entirely different direction; namely, that the incrustation represents suppressed formations of the order of the Hülle cells (p. 739). One is struck at the bulk of the incrusting matter enclosing the delicate filament that presumably produced it;[28] it is tempting, indeed, to assume that products of the microorganism have diffused outward and coagulated or otherwise hyalinized surrounding fluids. This theory deserves serious consideration with the others.

Conclusion in Re Incrustment.—It appears, thus, that incrustment of fungus cells in mammalian tissue can be brought about in more than one way:

1. Incrustment is a measure of resistance against adverse environment (this is illustrated in Torula histolytica); or, if the situation is viewed in a less vitalistic light it is due to the action of diffusion products (coagulating?) of the cell that provokes the deposit of surrounding fluids of other substances on the cell membrane.

2. It is an accompaniment of reproductive processes. The reproductive structure that it accompanies may be (*a*) developed fully, as with Coccidioides immitis, or (*b*) suppressed. Of this, final proof is lacking, but the Hülle cells of Aspergillus resemble forms seen in human tissue and may be tentatively classified, together with radiate aspergillotic forms under this heading.

It is appreciated that the first and second possibilities are interrelated to a certain extent, because the onset of adverse conditions is often the factor that initiates reproductive formation of cysts. However, the possibility of the absolute independence of the environmental factor from the reproductive factor, and the acquirement of marked and additional morphologic changes when incrustment of the latter type succeeds on that of the former type justify their separation.

Radiate (per Se) Effects.—The radiate or quasiradiate effect as it appears in these different forms of incrustment is contingent on at least three different circumstances. 1. In the torula (histolytica) cited, it was due to radial condensation within a common hyaloid stratum; it was not radiate in point of (configuration of) mass, but only in point of coloration (and perhaps also of chemistry). 2. With Coccidioides immitis and the fungus of the capybara, the capsule occurs not as a shell

28. Bayne-Jones' illustration clearly depicts the filament extending as the axis of the club, in culture.

of uniform thickness, but as a covering of radiating denticulations or even of elongated rays. 3. With Actinomyces it would be expeditious to explain the radiation simply as incidental to the radiate arrangement of mycelial filaments common to colonies of fungi in general, the hyaloid incrustment being continued like a coat of ice over the surface of the colony and its projecting terminal hyphae. Actually, such hyphae can seldom be demonstrated in the axis of a club, although Magrou [6] figured them for Botryomyces. However, in the light of what the fungus in the capybara showed as to the capacity of a solitary hypha to develop multiple radiations, it is now in order to strengthen the concept that the radiations of Actinomyces need never have contained central filaments but consisted of solid incrustment substance which was independently radiate from the first.

Calcification.—This may complicate true mycologic incrustation; not only does this modify staining reactions, but the thickening may be exaggerated or distorted. This occurred in the case of Kaposi's sarcoma cited. Certain blastomycetoid bodies occurring in a sarcoma-like lesion and in lupus vulgaris exhibited such concentric effects that they resembled psammoma bodies (Weidman and Douglas [29]). The much debated Gamna-Gandy bodies of African splenomegaly [30] are also in point. In all of these cases there is a question as to the genuineness of their fungous nature; elastic fibers are notoriously liable to calcification, and thus mimic calcified hyphae. The color plates of Boyce are most welcome in this dilemma, because they demonstrate filaments (in experimentally inoculated animals) with thickened, basic-stained walls within giant cells analogous to or identical with, at least morphologically, some of the "unknowns" cited. Boyce [12] enables one to diagnose hyphae within giant cells more confidently (see his fig. 8).

Classification of Incrustment.—The tabulation appended is on a morphologic basis; it is designed to show the range as to (1) quantity, (2) configuration (diffuse or radiate) and (3) species of fungus involved.

A. Radiation effect absent

1. Gloea formation (Botryomyces [6])
2. Capsule formation (B. mucosus-capsulatus, Torula histolytica [14]), Saccharomyces hominis [13]

29. Weidman, F. D., and Douglas, H. R.: Arch. Dermat. & Syph. **3**:743, 1921.

30. da Fonseca, O., and de Area Leao, A. E.: Mem. do Inst. Oswaldo Cruz, Aug. 31, 1928, supp. 1, p. 10. Symmers, D.; Gettler, A. O., and Johnson, W. M.: Surg., Gynec. & Obst. **28**:58, 1919. Nanta, E., and Pinoy, P.: Presse méd. **36**: 579, 1928.

3. Granular projections on cell membranes
   (*a*) Conidia and fuseaux of sundry dermatophytes (Achorion, Microsporon [17])
   (*b*) Madurella
   (*c*) Fürbringer's "involutive conidiophores" [31]

B. Radiation effect present
   1. A staining reaction: radiations not due to radial arrangement of incrusting substance, but to radially distributed variations in staining reaction (T. histolytica)
   2. Incrusting substance arranged radially [32]
      (*a*) No clubs. The matrical substance is more or less finely granular; its granules are arranged radially or in striae (some members of Actinomyces)
      (*b*) Clubs at periphery extend radially,[33] either completely around periphery (Actinomycosis, Actinobacillus,[26] Aspergillus) or incompletely around periphery (Oidium,[6] Actinomycosis)
      (*c*) Incrusting substance calcareous; radiation effect due to hyphae (Tonsillar and lachrymal calculi Kapsenberg [34])

SUMMARY AND CONCLUSIONS

In the lungs of a capybara a radiate form of fungus developed which was definitely different from that of actinomycosis both in certain features of its general morphology and in the identity of the fungus at its basis. While the fungus could not be classified with finality (on account of absence of cultures), it is suspected that it belongs to Aspergillus.

The infection was possibly acquired during an epizootic of aspergillosis among nearby penguins.

Since the radiate effect was found to be due to hyaloid material deposited on the exterior of the mycelium, the opportunity was taken to compare and analyze such deposits on fungi in general, both in culture and in tissue. As they occur in culture, it is concluded that

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31. Fürbringer: Virchows Arch. f. path. Anat. **66**:330, 1876.

32. The reactive host cells immediately adjacent to the radiate fungus are often arranged radially-strially, adding to the radiate effect. In absence of incrustment or matrical substance, radiation effects may still be met: mycelial hyphae arranged radially in tissue as they are in culture (Davis' actinomyces-like "grains" of tonsils [J. Infect. Dis. **14**:144, 1914], Boyce's [12] aspergillosis of human lung, Mycobacterium tuberculosis, M. diphtheriae).

33. Clubs may be feathery in form or show lateral spinules. In no case are all of the clubs spinulose; commonly only a few are thus affected (Oidium,[6] Botryomyces,[6] the capybara's Aspergillus).

34. Kapsenberg, G.: Tijdschr. v. vergelijk. geneesk. **9**:249, 1923.

those occurring in tissue, as in actinomycosis and aspergillosis, are not deposited from the surrounding tissue. The process is not analogous to the incrustments occurring in calcification.

Incrustment of fungus organisms in tissue involves a wide range of species-bacteria, streptothrixes, yeastlike forms and aspergilli. In addition, a radiate arrangement of such more or less matrical material can likewise occur in a variety of species (Actinomyces, Actinobacillus, Aspergillus). Fungus in a radiating form is not peculiar to or pathognomonic of actinomycosis; it serves only to focus attention on a particular group of micro-organisms, numerically small, but taxonomically widely distributed.

While the radiations are generally club-shaped, they may have more or less rectilinear sides, be spicular or otherwise depart from the conventions expressed in the radiate fungus Actinomyces bovis.

A table or key is submitted in which an attempt is made to classify the different expressions of incrustment according to morphology and species concerned.[35]

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35. Histologic sections of the lung of the capybara are deposited at the Army Medical School, Washington, D. C. (no. 36460), at the Laboratory of Comparative Pathology, Philadelphia Zoological Garden (no. 9998), and at the Laboratory of Dermatological Research, University of Pennsylvania (no. 2226).

TISSUE CHANGES FOLLOWING CONTINUOUS INTRAVENOUS INJECTION OF EPINEPHRINE HYDROCHLORIDE INTO DOGS

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It is the purpose in this paper to describe certain tissue changes that occurred in dogs following the intravenous administration of epinephrine hydrochloride at constant low rates over relatively long periods of time. Chemical data obtained in the study of several of the dogs have been presented in a previous paper.[1]

Consistent histologic changes were demonstrated in the liver, kidneys, hypophysis and adrenal glands. None were found in the spleen, striated muscle, smooth muscle, lungs, aorta or pancreas. The results obtained from staining sections of striated muscle for glycogen were inconclusive and could not be interpreted. Because of the lack of adequate controls of known age, the changes in the thymus could not be regarded as due to the injection of epinephrine hydrochloride and are therefore not included.

As far as can be determined, any tissue changes previously reported have occurred as the result of repeated injections of large amounts of epinephrine hydrochloride. In this connection, the work of Drummond [2] and that of Herter and Richards [3] may be mentioned. Acute changes such as congestion, hemorrhage and edema were prominent in their experiments. Drummond, giving from 10 to 15 cc. of 1:1,000 solution at a time, found no changes in the pancreas, spleen or adrenal glands. In the kidneys, he described widespread cloudy swelling in the lining epithelium of the convoluted tubules. In the liver, he noted central lobular necrosis and fatty changes in the cells in the middle zone of the lobule. The lungs were edematous, and an occasional polymorphonuclear leukocyte was found in the fluid. Herter and Richards described focal necroses in the pancreas and destructive changes in the islets following intraperitoneal injection of a single fatal dose of epinephrine hydrochloride.

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From the Department of Medicine, Rush Medical College of the University of Chicago.

1. Samson, P. C., and Jacobs, H. R. D.: Am. J. Physiol. **99**:433, 1932.
2. Drummond, W. B.: J. Physiol. **31**:81, 1904.
3. Herter, C. A., and Richards, A. N.: M. News **80**:201, 1902.

METHODS

Injections.—The apparatus used for the injections has been described by Jacobs.[4] Under local anesthesia, a cannula was inserted into the jugular vein of the dog, and epinephrine diluted with physiologic solution of sodium chloride was injected continuously at rates considered to be well within the maximum physiologic rate of secretion of the adrenal glands (Cannon and Rapport [5] and Kodama [6]). The rates of injection used in the present investigation were from 0.001 to 0.002 mg. per kilogram per minute (0.06 to 0.12 mg. per kilogram per hour), based on the original weight of the dog.

Medium-sized dogs of both sexes were used. They were unrestricted except by the collar and chain of the apparatus. They were given no food during the injection, but were allowed water as desired. At the end of the experiment, the dogs were killed, and a postmortem examination was made immediately. Tissues were fixed at this time for subsequent microscopic examination.

A commercial 1:1,000 dilution of epinephrine hydrochloride was used.

Fixation and Staining.[7]—For general survey, tissues were fixed in stock Zenker's solution or Zenker's solution plus solution of formaldehyde and paraffin blocks prepared according to the usual procedure. Sections were cut from 6 to 8 microns thick, made adherent by the albumin fixative method, stained with Delafield's iron-hematoxylin and counterstained with aqueous eosin.

For more detailed observation, the following stains were used: (1) Altmann's aniline-water-acid-fuchsin and aqueous methyl green on sections of pancreas, hypophysis and adrenal gland; (2) Mallory's reticulum stain on sections of hypophysis and aorta, and (3) toluidine blue, alone and with aqueous safranin, on sections of adrenal gland.

The fats were preserved in certain tissues by fixation with a diluted solution of formaldehyde, U. S. P. (1:10). Sections were cut on the freezing microtome and stained with an acetone solution of sudan III, followed by hematoxylin.

For the detection of glycogen, tissues were fixed in absolute alcohol. Sections were cut from paraffin blocks and stained with Best's carmine mixture, with the use of hematoxylin and a nuclear stain.

In addition to the fixative agents mentioned, pancreatic tissue was fixed in trinitrophenol-formaldehyde solution (so-called picro-formol [7a] and in acetic-osmic-bichromate solution (as used by Bensley [8]). Bowie's stain [9] was employed on the sections. The sections were removed from the staining solution at the end of

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4. Jacobs, H. R. D.: J. Lab. & Clin. Med. **16**:901, 1931.

5. Cannon, W. B., and Rapport, D.: Am. J. Physiol. **58**:308, 1921.

6. Kodama, S.: Tohoku J. Exper. Med. **4**:166, 1923-1924.

7. For a complete description of the fixative agents and stains used, see the following: Warthin, A. S.: Practical Pathology, ed. 2, Ann Arbor, Mich., George Wahr, 1921. Mallory, F. R., and Wright, J. H.: Pathological Technique, ed. 6, Philadelphia, W. B. Saunders Company, 1913. Lee, B.: The Microtomist's Vade-Mecum, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1928.

7a. The solution to which this term was applied by P. Bouin is made up as follows: trinitrophenol saturated aqueous solution, 75 parts; solution of formaldehyde, 25 parts; acetic acid, 5 parts.

8. Bensley, R. R.: Am. J. Anat. **12**:297, 1911.

9. Bowie, D. J.: Anat. Rec. **29**:57, 1924-1925.

twenty-four hours, blotted with absolute alcohol, and differentiated in pure oil of cloves. The differentiation was controlled under the microscope.

In staining for elastic fibers, Weigert's resorcin-fuchsin was used, following lithium carmine.

PROTOCOLS

Continuous injections of epinephrine hydrochloride were made in one male and five nonpregnant female dogs. The length of the injections varied from 120 to 289 hours. The amount injected varied from 59 to 246 mg. The average loss in weight of the six dogs was 159 Gm. per day. Control tissues were taken from: (1) ten normal dogs (six females and four males); (2) two dogs into which physiologic solution of sodium chloride had been injected continously for fourteen and fifteen days, at rates of from 20 to 50 cc. per hour. The average loss in weight of the latter two dogs was 191 Gm. per day. In three of the experimental dogs, a terminal pulmonary infection developed. They are included for the reason that the tissue changes in the other organs were similar to those in the rest of the dogs given injections.

RESULTS

Liver.—The changes in the liver were all of the same type, but were not in proportion to the amounts of epinephrine hydrochloride injected. Grossly, the livers were smaller and more friable than normal and showed a distinct yellow mottling on cut surfaces.

A comparison of sections from the different livers stained with hematoxylin and eosin showed that in some the change was limited to a slight degree of vacuolization in the cells immediately surrounding the central vein of the lobule. In those livers showing the most change, nearly all the cells were vacuolated. The cytoplasm of the more central cells of the lobule was entirely replaced, only cell outlines being visible. All nuclei stained well (fig. 1).

In sections of liver stained with sudan III following fixation in formaldehyde, the vacuoles and clear spaces were filled with fat. The degeneration was a fatty change and not necrosis. No glycogen was demonstrable by staining in any of the animals. Since the livers of the control dogs, into which physiologic solution of sodium chloride had been injected continuously, contained enough glycogen to give a faintly positive staining reaction, even after two weeks without food, it is probable that if the livers of the experimental animals contained glycogen, it was present in much less than normal amount.

Kidneys.—On gross examination, the kidneys were generally paler than normal. The capsule stripped easily. The chief gross changes were in the cortex. In three of the animals there was a yellowish band in the middle zone of the cortex, and in one, the whole cortex was distinctly yellow in contrast with the normal pink of the medulla.

The microscopic changes varied in amount, but were of the same nature in all. They were of the type found in nearly every "normal" dog, but were much greater in degree. Stained with hematoxylin and eosin, the different kidneys showed varying degrees of vacuolization in the cells lining the limbs of Henle's loop. In many of the cells, the cytoplasmic area was entirely clear. The nuclei stained well. Congestion was generalized in the capillaries of the cortex. The convoluted tubules and glomeruli appeared normal (fig. 2). Sections stained with sudan III demonstrated a fatty change in the cells lining the limbs of Henle's loop. The change was marked throughout the cortex, but ended abruptly at the junction of the cortex and medulla. The orange streaks were visible grossly on the slide.

A small amount of fat was occasionally found in the cells of the collecting tubules, a condition not seen in any of the sections from normal animals. No other changes were noted in the medulla. Glycogen degeneration was not demonstrated.

Hypophysis Cerebri.—There seemed to be no variation in the size either of the anterior lobe or of the hypophysis as a whole when glands from the experimental animals were compared with normal glands. However, no exact weights were obtained. In sections that were stained with hematoxylin and eosin, the anterior

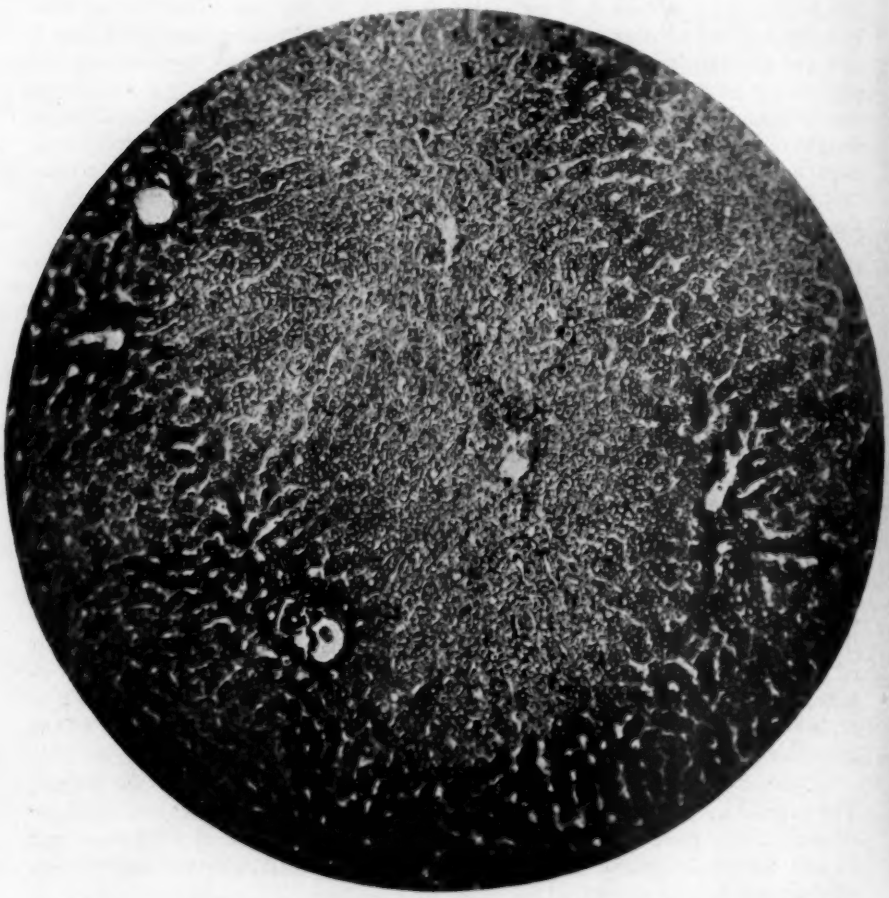

Fig. 1.—A section of liver stained in hematoxylin and eosin and magnified 80 times, from a dog that received 59 mg. of epinephrine hydrochloride in 184 hours. It shows extensive vacuolization of the central lobular cells and partial vacuolization of the more peripheral cells.

lobe tended to take a heavy eosin stain and showed in general more nuclei per high power field than were found in the controls. The blood spaces did not appear to be consistently more dilated or more collapsed than normal.

Examination of sections stained with 1 per cent aniline-acid-fuchsin and 0.5 per cent aqueous methyl green showed that there were consistent changes in the cellular elements of the pars anterior in all the experimental animals.

The chromophobe cells showed a considerable loss of secretory substance, which resulted in cytoplasmic shrinkage. This appeared to be the mechanism chiefly responsible for the increased number of nuclei seen in a single field.

The alpha cells were more intensely acidophilic and were present in greater numbers. They did not seem to be increased in size. No mitotic figures were observed. The alpha cells varied in their affinity for fuchsin. A few stained faintly, but the greater proportion were hyperacidophilic. The deeply staining

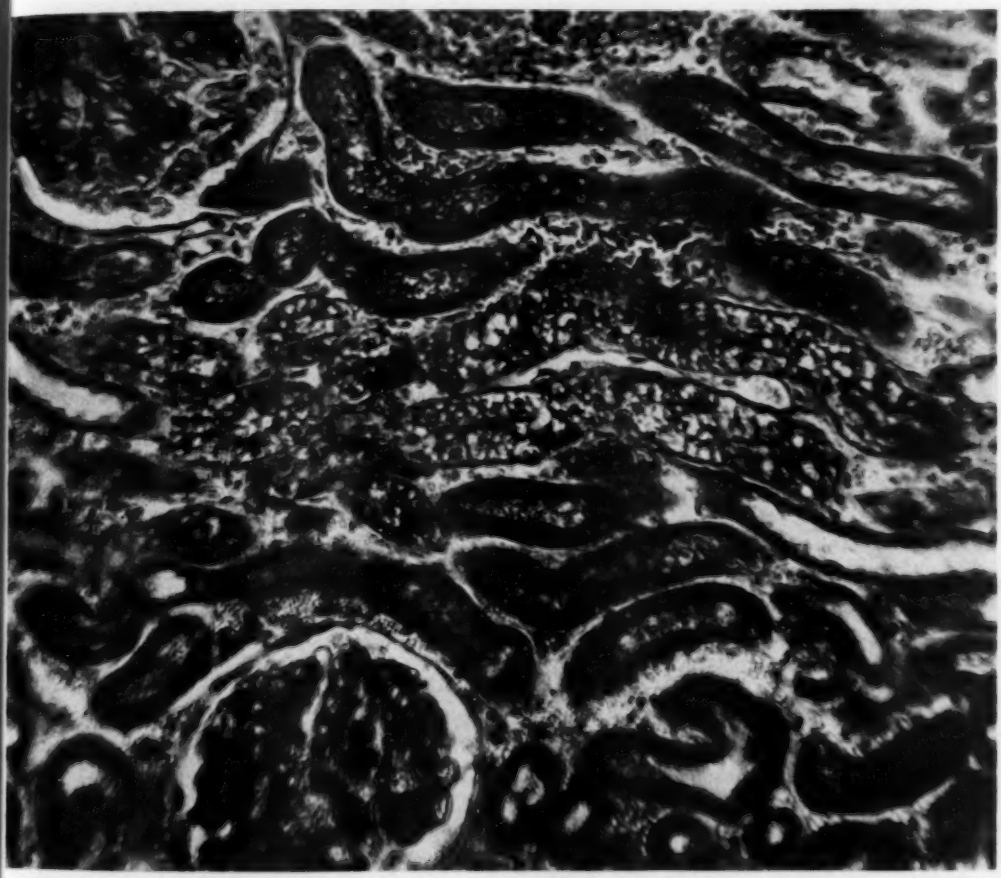

Fig. 2.—A section of kidney stained with hematoxylin and eosin and magnified 290 times, from a dog that received 69 mg. of epinephrine hydrochloride in 164 hours. It shows vacuolization of the cells lining the limbs of Henle's loop.

alpha cells were numerous in all parts of the anterior lobe and were found in what appeared to be definite layers surrounding many of the blood spaces (fig. 3). In the experimental animals, this condition was generalized throughout the anterior lobe and was conspicuous. In the normal animals, the alpha cells were found for the most part in the region bordering the pars intermedia, and the tendency to layer formation around the blood spaces was occasionally noted.

Kojima [10] (quoted by Cowdry [11] and Maximow [12]) gave epinephrine to animals in food. He reported an enlargement of the anterior lobe and an increase in both the size and the number of the alpha cells. On the contrary, Igura,[13] examining rats after the injection of epinephrine hydrochloride described a decrease in the size and number of the alpha cells and an enlargement of the chief cells.

In sections from the experimental animals stained with Mallory's reticulum stain, the basophilic cells appeared to be smaller and diminished in number; in fact, they were often difficult to find.

Adrenal Glands.—Grossly, the adrenal glands appeared normal in size and consistency. The amount of congestion varied, but was within normal limits. There were no gross hemorrhages. The hematoxylin and eosin stains were normal. A few red blood cells were scattered along the cell columns of the cortex. Sections stained with sudan III did not show any alteration in the quantity, type or distribution of the lipoid substance in the cortex, when compared with the normal. No glycogen degeneration was demonstrated.

Borberg [14] and Ogata and Ogata [15] showed that when sections of adrenal tissue are stained with toluidine blue, the depth of green that develops in the medulla is roughly proportional to the amount of epinephrine or preepinephrine substance present. Such tissues must be fixed in some acid-free chromate solution, since acid seems to interfere. The latter authors believed the reaction to be a simple reduction of the epinephrine on the chromates.

Sections of adrenal glands were fixed in Zenker's solution plus solution of formaldehyde and stained with 0.5 per cent aqueous toluidine blue. In all cases, the depth of green that developed was less than that found in the normal controls. In the adrenal glands from two of the experimental animals, only the faintest traces of green could be found in the medulla. Such findings agree with those of Tournade and Chabrol,[16] and Molinelli,[17] who concluded from chemical data that injection of epinephrine hydrochloride results in diminution of the endogenous secretion.

In staining with toluidine blue it was found better not to counterstain with safranin and dehydrate in alcohol, as some authors recommend. As pointed out by Ogata, alcohol causes toluidine blue to fade. After the excess toluidine blue had been washed out, the slides were blotted with successive applications of xylene until they became translucent; thus the necessity for using alcohol in dehydration was avoided.

A consistent change in staining reaction that was rarely found in the normal control was demonstrated in certain cells of the adrenal cortex of the experimental animal when sections were stained with 1 per cent aniline-acid-fuchsin and 0.5 per cent aqueous methyl green. These cells were similar to the surrounding cells

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10. Kojima, M.: Quart. J. Exper. Physiol. **11**:319, 1917.

11. Cowdry, E. V., in Barker, L. F., and others: Endocrinology and Metabolism, Philadelphia, W. B. Saunders Company, 1922, vol. 1, p. 705.

12. Maximow, A. A.: Text-Book of Histology, finished and edited by William Bloom, Philadelphia, W. B. Saunders Company, 1930, p. 691.

13. Igura, S.: Abstr., Ber. ges. Physiol. u. exper. Pharmacol. **44**:104, 1928; Chem. Abstr. **22**:2987, 1928.

14. Borberg, N. C.: Skandinav. Arch. f. Physiol. **28**:91, 1912.

15. Ogata, T., and Ogata, A.: J. Exper. Med. **25**:807, 1917.

16. Tournade, A., and Chabrol, M.: Compt. rend. Soc. de biol. **94**:535, 1926.

17. Molinelli, E. A.: Compt. rend. Soc. de biol. **95**:1084, 1926.

in size and shape and were scattered irregularly throughout the cortex. Mitosis was not observed. The cytoplasm was somewhat coarsely granular and intensely acidophilic, staining red in aniline-acid-fuchsin and blue in toluidine blue. The nuclei were smaller and somewhat more compact than those of the surrounding cortical cells and gave a metachromatic staining reaction. In aniline-acid-fuchsin and methyl green, they stained red or purple, and in toluidine blue and safranin, blue or red, depending on which stain was employed most intensely.

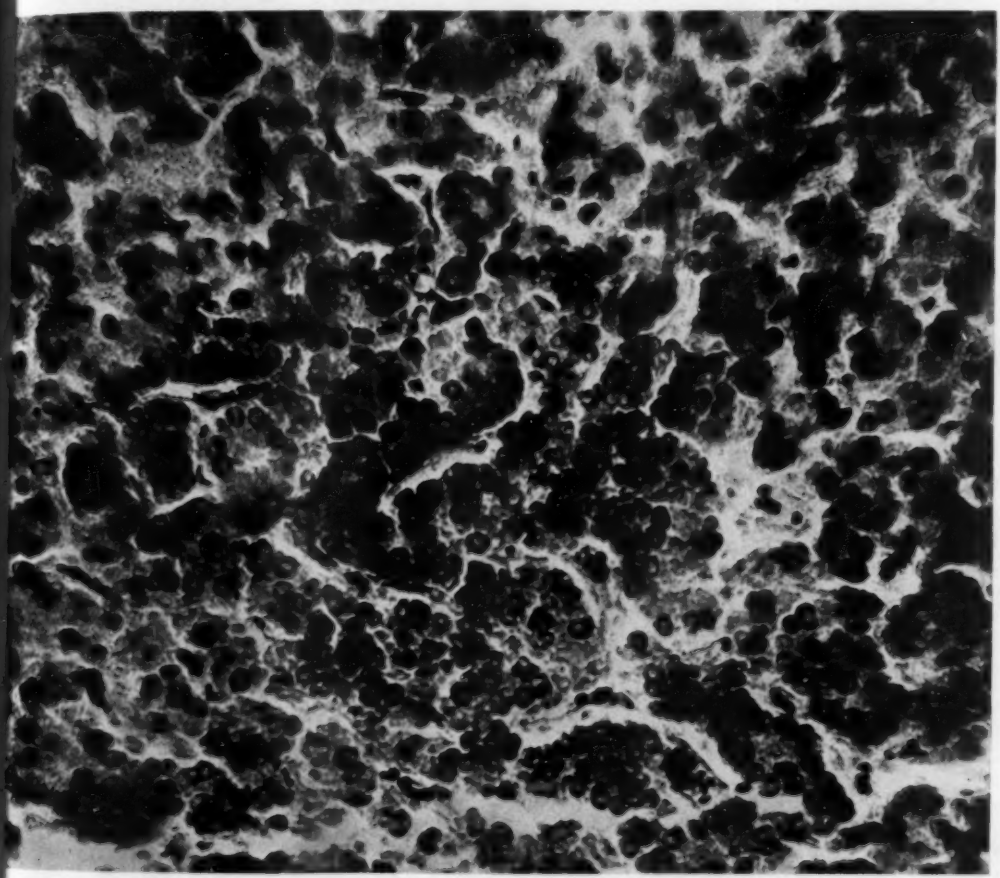

Fig. 3.—A section of hypophysis stained with aniline-acid-fuchsin and methyl green and magnified 320 times, from a dog that received 112 mg. of epinephrine hydrochloride in 272 hours. It shows by the dark cells the increased number of hyperstaining alpha cells. The distribution of alpha cells in layers around the blood spaces is particularly conspicuous.

Cardiovascular System.—In five dogs, the heart was found in systole. In the other, it was in diastole. In three of the animals, there were small punctate endocardial hemorrhages in the wall of the left ventricle, chiefly around the base of the papillary muscle. In three, the wall of the aorta appeared yellower than normal. In no case was there evidence in any vessel of intimal plaques or calcification.

Hematoxylin and eosin stains of the myocardium were normal. Weigert's resorcin-fuchsin stain showed that the internal elastic lamina of the coronary vessels was uninterrupted. No patholic changes were found in the smaller arteries and veins. Since Josué [18] in 1903 first described aortic sclerosis following repeated injections of epinephrine hydrochloride, many authors have reported experimental atheromatous lesions produced by this method. The literature on this subject has been reviewed by MacCallum.[19] Lesions have been produced successfully in rabbits only. Pearce and Stanton [20] attempted to reproduce similar changes in the aorta of a dog by the injection of epinephrine hydrochloride. They gave about 9 mg. over a period of a month.

Although in the aortas from the experimental animals occasional areas were found where there were slight fragmentation of elastic fibers and some increase in connective tissue (Mallory's reticulum stain) in the outer third of the media, similar areas were also found in normal controls. The connective tissue was not hyalinized, and there was no increase or decrease in cellular elements in the questionable areas. No calcium or fatty deposits were noted. It was concluded that no definite changes occurred in the aorta that could be attributed to the action of the injected epinephrine hydrochloride.

Pancreas.—Because of reports in the literature by Miyairi,[21] who described islet hypertrophy and hyperplasia and a decrease in granule content of the islet beta cells following injection of epinephrine hydrochloride, and by Igura,[13] who described atrophy of the pancreas cells as the result of administration of epinephrine, the pancreas was studied with especial care. This phase of the work was carried on under the supervision of Prof. R. R. Bensley of the University of Chicago, who also reviewed the sections of the hypophysis and aorta. In several of the dogs, serial sections from 3 to 5 microns thick were cut from different blocks of pancreatic tissue fixed in the fluids outlined under "Methods." These were stained both with Bowie's solution and with aniline-acid-fuchsin and methyl green.

No histologic evidence was found that would indicate either islet degeneration or the formation of new islets from acinar tissue. Islet hypertrophy or hyperplasia was not demonstrated. The granule content of both the alpha and the beta islet cells appeared to be within normal limits in all the experimental animals when sections were compared with normal controls. The zymogen granule content of the acinar cells also appeared to be normal.

COMMENT

It is evident that the continuous intravenous administration of epinephrine hydrochloride over relatively long periods of time, even when the drug is injected at rates considered well within the maximum physiologic rate of secretion of the adrenal glands, has a deleterious effect on the animals used. There appears to be an individual susceptibility to epinephrine, since, in spite of the fact that the rate of injection was about the same for each animal, the degree of tissue change was not necessarily in proportion to the amount of epinephrine hydrochloride administered.

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18. Josué, O.: Presse méd. **11**:798, 1903.
19. MacCallum, W. G.: Physiol. Rev. **2**:70, 1922.
20. Pearce, R. M., and Stanton, E.: J. Exper. Med. **8**:74, 1906.
21. Miyairi, S.: Proc. Imp. Acad. **3**:702, 1927.

In watching the behavior of the animals given a continuous injection of epinephrine hydrochloride, and of those given an injection of physiologic solution of sodium chloride only, it was noted that in the former group the dogs became quiet rather early in the experiment and apparently became weaker as the experiment progressed, the weakness being most marked in those animals that afterward showed the greatest tissue change. The control animals, on the other hand, showed surprisingly little weakness and no changes in behavior even after continuous injection and starvation for a period of two weeks.

The action of epinephrine seems in part to be a toxic or a degenerative one and, as might be expected, the liver and kidneys show morphologically the greatest damage.

The reason for the cell changes in the anterior lobe of the hypophysis is not clear, since the exact function of the different cells is not known. There was an evident increase in the number of acidophilic cells as seen in sections from the experimental animals. A relative increase resulted from the loss of secretory substance of the chromophobe cells, which in itself appeared to follow the injection of epinephrine hydrochloride. The belief that there may have been an actual, as well as a relative, increase in the number of alpha cells, particularly of the hyperstaining type, is based on the following observations: It was found that, in addition to the large number of hyperacidophilic cells seen in each microscopic field, there were single cells and groups of cells scattered irregularly throughout the sections in which the cytoplasm was very faintly acidophilic. All gradations of intensity in staining were found. Because of morphologic similarities, these cells were all believed to be alpha cells in various stages of development. Since no mitotic figures were observed, it seems plausible that there was a transition to acidophils from cells already present in the anterior lobe, perhaps similar to the transition described by Collin,[22] the result of secretory activity.

Whether the immediate antecedents of the faintly staining acidophilic cells were undifferentiated cells, chromophobes or possibly basophils (since these were decreased markedly in the experimental animals), could not be decided from the evidence at hand. In addition, the conspicuous distribution of the hyperstaining alpha cells in more or less definite layers surrounding the blood spaces strengthened the view that many of these cells had but recently acquired the acidophilic characteristics. Such a distribution might also be taken as evidence that some substance in the blood stream, presumably epinephrine, was responsible for the increase in the number of acidophilic cells. It is impossible to say whether the cell changes in the anterior lobe were the result of stimulation or of toxic action of the injected epinephrine hydrochloride.

22. Collin, R.: Compt. rend. Soc. de biol. **102**:853, 1929.

In view of the definite changes that have often been reported as taking place in the aorta of the rabbit following the administration of epinephrine hydrochloride it is surprising that no changes were found in the aorta of the dog. It is known that sclerosis and calcification of the aorta occur spontaneously in the rabbit, and that this condition is practically never found in the dog.

While one can discuss, from a theoretical point of view, the possible reasons for the lack of change found in the aorta of the dog following the administration of epinephrine hydrochloride, further experimentation must be done before definite conclusions can be drawn.

The aorta of the dog may have an intrinsic immunity to the action of epinephrine. It may be that the liver of the dog is more efficient in destroying epinephrine than that of the rabbit and is more injured thereby.

Kajimura [23] showed that the injection of epinephrine hydrochloride into rabbits causes hypercholesteremia, followed by fatty deposits and sclerotic changes in the aorta. It is not known whether the injection of epinephrine hydrochloride causes hypercholesteremia in the dog.

It should be determined whether or not epinephrine produces effects on the vasa vasorum in the rabbit and dog that are similar. Hartman and his co-workers [24] obtained a vasodilatation in several species of mammals following the injection of moderate amounts of epinephrine hydrochloride, but obtained only vasoconstriction in rabbits. They concluded that rabbits did not possess an epinephrine vasodilatation mechanism. Somewhat later, Ravault and Bouysset,[25] using rabbits, injected trypan blue both alone and immediately preceding the injection of epinephrine hydrochloride. In the latter case, the coloration of the outer zone of the media was much decreased. They concluded that there was constriction of the vasa vasorum following the injection of epinephrine hydrochloride, with consequent interference with the nutrition of the aortic wall. They produced sclerotic changes in the same region by numerous injections of epinephrine hydrochloride, which they believed were based on nutritional disturbances. To my knowledge, similar experiments have not been performed in the dog.

Whatever the reason, it is probable that the marked arterial changes that have been reported to follow the injection of epinephrine hydrochloride in the rabbit cannot be duplicated in the dog.

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23. Kajimura, S.: Okayama-Igakkai-Zasshi **41**:1854, 1929.

24. Hartman, F. A.; Kilborn, L. G., and Lang, R. S.: Endocrinology **2**:122, 1918.

25. Ravault, P. P., and Bouysset, C.: Compt. rend. Soc. de biol. **99**:828 and 829, 1928.

It is possible that the cell changes described in the adrenal glands may be the result of a toxic action of the injected epinephrine hydrochloride on the adrenal cortex.

SUMMARY

Epinephrine hydrochloride was administered intravenously to dogs at constant rates over relatively long periods of time (up to thirteen days). The amounts injected varied from 59 to 246 mg.

Consistent tissue changes were found in the liver, kidneys, hypophysis and adrenal glands. The pancreas, aorta, spleen, smooth and striated muscle and lungs were found unchanged. The liver showed an intracellular fatty change. In the cases in which the liver was the least affected, small droplets of fat were deposited in the cells surrounding the central vein of the lobule. With more advanced change, the peripheral cells of the lobules contained fat droplets, and the cytoplasm of the central cells was almost entirely replaced by fat. The kidneys showed a fatty change in the cells of Henle's loop and rarely in the cells of the collecting tubules. In the anterior lobe of the hypophysis there was loss of the secretory substance of the chromophobe cells. The alpha cells showed in general a hyperacidophilic staining reaction, appeared to be increased in number and showed a conspicuous distribution in layers around many of the blood spaces. There was a decrease in the number and size of the basophilic cells.

In the cortex of the adrenal glands, many of the cells showed an altered staining reaction, and there was apparently a decreased endogenous secretion of epinephrine as the result of the injection of epinephrine hydrochloride.

It has been suggested that the action of epinephrine on certain animal tissues is in part a toxic or a degenerative one.

AVITAMINOSIS

III. PATHOLOGIC CHANGES IN TISSUES OF THE ALBINO RAT DURING EARLY STAGES OF VITAMIN A DEFICIENCY

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During the period from 1913 to 1922 it was generally assumed that deficiency of vitamin A produced only decline of body weight, frequently associated with xerophthalmia (first described by Osborne and Mendel [1] in 1913) and with respiratory disturbances (first observed by McCollum [2] in 1917). No other pathologic changes were recognized until 1922, when Mori [3] found cornification of the mucosa of the larynx and trachea and of the ducts of the submaxillary, sublingual and parotid glands. Mori referred to the change as keratinization. He attributed xerophthalmia to the drying of the epithelium due to the hypofunction of the lacrimal gland, the secretion of which keeps these epithelial surfaces moist

In 1922, Evans and Bishop [4] reported peculiar changes in the estrual rhythm on a ration deficient in vitamin A. They stated:

> It consists in the prolongation of the oestrus desquamative change in the vaginal epithelium, the smear consisting chiefly, if not exclusively, of the cornified cells which in normal individuals characterize the actual periods of oestrus and ovulation only, but which in the case of animals showing vitamin A deficiency occur throughout the entire period of acute deficiency.

Evans and Bishop reported that the preponderance of cornified cells in the vaginal epithelium was the most delicate and the first sign of vitamin A deficiency that they encountered, which became apparent long before cessation of growth took place.

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Research Paper no. 240, Journal Series, University of Arkansas.
From the Department of Pathology, School of Medicine, University of Arkansas, Little Rock, and the Department of Agricultural Chemistry, University of Arkansas, Fayetteville.

1. Osborne and Mendel: J. Biol. Chem. **16**:423, 1913.
2. McCollum: J. A. M. A. **68**:1379, 1917.
3. Mori: Bull. Johns Hopkins Hosp. **33**:357, 1922.
4. Evans and Bishop: J. Metab. Research **1**:10, 1922.

In 1925, Wolbach and Howe [5] confirmed the results of Mori and, in addition, found metaplastic changes in the pancreatic duct and renal pelvis. Metaplasia was found of the cylindric, cuboidal or transitional type of epithelium to the squamous, keratinizing type. They attributed these changes to vitamin A deficiency. They found the same changes in the salivary glands as Mori, but disagreed with the latter investigator in the claim that the secretions of these glands induced the metaplasia.

When Mori and Wolbach and Howe carried out their studies, vitamin A was not as yet differentiated into vitamins A and D, and the rations of these workers were therefore deficient in D as well as in A. Therefore, in 1927, Goldblatt and Benischek [6] reported their observations on diets deficient only in vitamin A, vitamin D having been furnished by irradiated cottonseed oil. They concluded that the metaplastic changes were as frequent and as great in rats on a diet deficient in vitamin A alone as in those on diets deficient in vitamins A and D. They also reported that, provided the vitamins were supplied, inanition, while producing atrophy of tissues, did not induce the metaplasia. They also noted the great frequency of abscesses at the base of the tongue.

In 1928, Green and Mellanby [7] reported that rats brought up on a diet deficient in vitamin A practically all died with infective or pyogenic lesions. In the control animals, receiving vitamin A, these lesions were absent. The presence of vitamin D did not prevent the resistance to infection. From their investigations they concluded that vitamin A is an anti-infective agent.

In 1929, Tyson and Smith [8] concluded that, in addition to metaplastic changes in various tissues, epithelial hyperplasia was striking in the tongue and renal pelvis, the hyperplasia in the latter overshadowing the keratinizing process. They stated that the metaplastic changes involved the following structures in order: the sublingual glands, the submaxillary glands and the epithelium of the renal pelvis as well as that of the trachea and bronchi. The tongue was regularly involved before xerophthalmia appeared. They also emphasized the existence of infection in vitamin A deficiency. They stated, "Infection is always present in the earliest stages and in late cases dominates the picture. No metaplastic activity has been seen without an accompanying infection, but infection has been observed in parts where metaplasia is absent."

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5. Wolbach and Howe: Proc. Soc. Exper. Biol. & Med. **22**:402, 1925; J. Exper. Med. **42**:402, 1925.

6. Goldblatt and Benischek: J. Exper. Med. **46**:699, 1927.

7. Green and Mellanby: Brit. M. J. **2**:691, 1928.

8. Tyson and Smith: Am. J. Path. **5**:57, 1929.

In 1923, Daniels [9] showed that in albino rats on diets deficient in vitamin A pyogenic infections developed in the sinuses and nasal cavities. These observations were later corroborated by Turner and his associates.[10]

Recently Green, Pindar, Davis and Mellanby [11] reported that vitamin A might be profitably used as a prophylactic agent against puerperal sepsis. Of a total of 550 pregnant women, 275 received the vitamin supplement, and 275 served as controls. "Of the 'vitamin treated' cases, 1.1 per cent, and of the controls, 4.7 per cent, developed the 'British Medical Association' standard of morbidity. The results classified on the basis of duration of pyrexia also suggested that the vitamin preparation increased the resistance of the puerperal women to infection."

The puzzling point in experimental research with reference to vitamin A is the criterion for the detection of the first signs of A avitaminosis. Some investigators claim that cessation of growth is the first expression of vitamin A deficiency, while other workers use the onset of ophthalmia as the standard. Evans and Bishop [4] claimed that prolongation of the cornified stage of the estrual cycle is the first manifestation of vitamin A depletion. Osborne and Mendel [12] found ocular symptoms in 69 of 136 rats on diets deficient in vitamin A, and Stephenson and Clark,[13] in 13 of 46 rats, while Sherman and Munsell [14] found an unmistakable disease of the eye in 85 per cent of their animals suffering from vitamin A deficiency. The latter investigators found distinct gatherings of pus in one or more of the glands near the base of the tongue in 76 per cent of the cases, and considered the base of the tongue as a characteristic seat of lesion in A avitaminosis. We found ophthalmia in 71 per cent of our pathologic animals. Recently, Honeywell, Dutcher and Ely [15] published the results of vitamin A investigations in which they employed two brands of yeast as a source of the vitamin B complex. With the use of one of these brands of yeast, the incidence of ophthalmia among the vitamin A deficient animals was only 20 per cent, but growth was poor. With the second brand of yeast, growth was good, but the incidence of ophthalmia was 100 per cent. They therefore suggested that "vitamin A may consist of two factors, one possessing anti-ophthalmic properties which tends to preserve normality of other epithelial tissues, and the other factor possessing the growth-stimulating properties usually ascribed to vitamin A."

9. Daniels: J. A. M. A. **81**:828, 1923.

10. Turner: Proc. Soc. Exper. Biol. & Med. **26**:233, 1928. Shurly and Turner: J. A. M. A. **94**:539, 1930. Turner, Anderson and Loew: J. Infect. Dis. **46**:328, 1930. Turner and Loew: J. Infect. Dis. **49**:244, 1931.

11. Green, Pindar, Davis and Mellanby: Brit. M. J. **2**:595, 1931.

12. Osborne and Mendel: J. A. M. A. **76**:905, 1921

13. Stephenson and Clark: Biochem. J. **14**:502, 1920.

14. Sherman and Munsell: J. Am. Chem. Soc. **47**:1639, 1925.

15. Honeywell, Dutcher and Ely: J. Nutrition **3**:491, 1931.

The purpose of our investigation was to determine whether during the early stages of vitamin A deficiency, as evidenced by incipient signs of ophthalmia, a prolongation of the cornified stage during estrum or a cessation of growth, there were any significant metaplastic changes in the respiratory and urinary tracts, the posterior part of the tongue and the salivary glands. Microscopic studies were also made of the liver, adrenal glands, thyroid gland, hypophysis, thymus, bone marrow, genitalia, spleen, lymph nodes, pancreas, skeletal muscle, skin, larynx, urinary bladder, aorta, stomach, intestines including the cecum, and heart. The weight of the adrenal glands, heart, spleen, kidneys and liver were taken in forty-two pathologic animals and nineteen controls. Histologic changes were studied in fifty-three animals deficient in vitamin A and in twenty-four controls.

TABLE 1.—*Rations Deficient in Vitamin A Component*

Component	Ration 1749	Ration 1769
Casein (purified)*	20	20
Salts no. 185 †	4	4
N. W. yeast	10	10
Lard	2	1
Butter fat	..	1
Dextrin	64	64

* Purified by several extractions with hot 95 per cent alcohol.
† McCollum and Simmonds: J. Biol. Chem. 33: 63, 1918.

VITAMIN A DEFICIENT DIETS USED; HISTOLOGIC TECHNIC.

The vitamin A deficient rations employed are listed in table 1. Ration 1749 was our standard vitamin A deficient diet. One per cent of butter fat was incorporated in ration 1769 so as to prevent the rapid onset of respiratory disturbances and thus to afford greater opportunity of detecting the incipient stages of A avitaminosis. Although the original plan was to deal only with early stages of this disease, advanced stages of vitamin A deficiency as characterized by marked ophthalmia were purposely allowed to develop in a number of animals so that a comparison might be made of the metaplastic changes in epithelial structures of various tissues during the early and later stages of A avitaminosis. As shown in table 2, the animals with marked lesions of the eyes showed a greater incidence of infection than the animals with incipient ophthalmia, although no marked differences had been observed in the extent of metaplasia.

The tissues were fixed immediately in Zenker's solution or in formaldehyde. After the Zenker fixation, they were stained by Giemsa's method according to the modification of Wolbach.[16] After fixation in formaldehyde, they were stained with hematoxylin and eosin.

16. Mallory and Wright: Pathologic Technic, ed. 8, Philadelphia, W. B. Saunders Company, 1924, p. 44.

OBSERVATIONS

Most of our findings are summarized in tables 2 and 3. The remainder are presented in abstract form in the text that follows.

Histologic Changes.—The histologic changes were similar in most respects to those described by other workers, especially those reported by Wolbach and Howe.[5] In almost every rat there were metaplastic changes in the posterior portion of the tongue, with abscesses, dilatation of ducts, atrophy or fibrosis. Metaplasia was more common in the respiratory tract than in the ducts of the salivary glands or in the genito-urinary tract. After the posterior portion of the tongue, the upper respiratory tract was most frequently affected. This metaplasia was usually present in localized regions. Pneumonia occurred in five animals. The sublingual glands were involved more frequently than the submaxillary glands. The parotid glands were affected only occasionally. Atrophy of acini of the sublingual and submaxillary glands was noted; also atrophy of lining cells of the respiratory tract. Two of the tracheae were infected, including the glands.

Urinary Tract: It was common to see keratinization localized in the pelvis of the kidney. The urinary bladder was frequently involved in the same manner. Infection was noted five times.

Liver: Fibrosis about the portal spaces with infiltration by eosinophils and small lymphocytic cells was noted frequently. This change was also found in one of the controls, but it was not as marked as in the animals deficient in vitamin A.

Adrenal Glands: There were no noteworthy microscopic changes.

Thyroid Gland: A few of the acini appeared collapsed with lack of colloid, but this was seen in a few of the controls. In several thyroid glands, the acini were small, but this change was also present in the controls. In only one gland was definite atrophy of the cells lining the acini observed. No changes occurred in the parathyroid glands studied.

Hypophysis: No significant changes were found.

Thymus: In one slide there was an extremely large Hassal corpuscle with desquamation in the center not unlike an epithelial pearl. Some of the cells of Hassall's corpuscles appeared larger in the deficient animals than in the controls, but we do not care to make a positive statement with the examination of a comparatively small number of thymuses.

Bone Marrow: No noteworthy changes were found in the bone marrow except those changes present in acute infection.

Female Genitalia: The ovaries and tubes did not have any significant changes, but it would be necessary to examine a larger number to come

TABLE 2.—*Pathologic Changes in Various Tissues of the Albino Rat in Vitamin A Deficiency*

Animal	Duration of Experimental Period, Days	Changes in Weight Last 12-15 Days of Experiment, Gm.	Posterior Part of Tongue	Salivary Glands	Respiratory Tract	Urinary Tract	Other Pathologic Changes
♀ 1	40	+ 6	MDI*	AM	AMI	..	Uterus, M; spleen, A
♂ 2	43	+ 5	MDF	....	....	..	Liver, F about portal spaces; spleen, A
♀ 3	43	+ 8	MDI	A	AM	M	Liver, F about portal spaces; spleen, A
♂ 4	43	+ 9	MD	....	A	..	Liver, F about portal spaces; peribronchial infiltration
♂ 5	47	— 3	MDI	....	AM	M	Testes, A; spleen, A; heart, F and infiltration
♂ 6	47	+41	MD	AM	AM	..	Liver, F about portal spaces
♀ 7	46	+ 3	MDI	AM	AM	M	Liver, F about portal spaces; peribronchial infiltration
♀ 8	46	+ 8	MDI	M	AM	M	Liver, F about portal spaces; spleen, A
♂ 9	47	+ 3	MDI	M	AM	..	
♀ 10	47	+ 3	MDI	AM	AM	M	Uterus, MI; spleen, A; pancreas, A; peribronchial F
♀ 11	47	—25	MDI	MA	AM	M	Liver, fat
♂ 12	47	—14	MDI	M	AM	M	Testes and spleen, A; peribronchial edema
♂ 13	40	+ 3	F	....	M	M	
♂ 14	33	+30	MDF	....	AM	..	Spleen, A
♂ 15	40	+15	MF	AM	A	..	Spleen, A; peribronchial edema and infiltration
♂ 16	40	+14	MDIF	M	AM	M	
♀ 17	39	+15	MD	AM	AM	M	Liver, F about portal spaces
♂ 18	39	+ 4	MD	A	AMI	M	
♂ 19	39	+13	MD	....	AMI	M	
♂ 20	39	+10	MDF	....	M	M	Testes, A
♂ 21	34	+25	MDI	AMI	M	..	Spleen, A
♀ 22	34	+22	MDF	MA	....	..	Liver, F about portal spaces
♀ 23	34	+20	MF	A	M	..	Spleen, A; peribronchial infiltration
♀ 24	34	+15	MDF	Edema	A	..	Liver, focal necrosis; peribronchial infiltration
♀ 25	50	+16	MF	....	AM	..	Spleen, A; peribronchial infiltration
♀ 26	39	+ 6	F	M	MA	..	Spleen, A; heart, F
♀ 27	50	+ 5	MFI	A	M	..	Liver, F about portal spaces; spleen A
♀ 28	39	+ 5	MDI	....	MA	..	Peribronchial infiltration
♀ 29	51	+ 5	MDF	MA	AMIP	..	Liver, F about portal spaces; spleen, A; bronchitis and pneumonia
♀ 30	47	+ 9	MDF	M	AM	M	Liver, F about portal spaces; peribronchial edema
♀ 31	47	— 1	MDIF	M	AMI	MI	Liver, F about portal spaces; spleen, A
♀ 32	38	+ 9	F	M	A	M	
♀ 33	36	+30	MD	A	....	..	Spleen, A; peribronchial infiltration
♀ 34	44	+11	MI	A	AM	..	Liver, focal necrosis and F about portal spaces
♀ 35	38	+ 1	F	....	MA	..	Heart, F; acute bronchitis and peribronchial infiltration
♀ 36	44	+10	M	M	AM	M	Liver, F about portal spaces; spleen, A
♀ 37	73†	—41	MDI	....	AMI	MI	Liver, fat; uterus, MI; heart, F; hair follicles of skin, A
♂ 38	62	—76	MDI	M	AM	MI	Liver, F about portal spaces; testes, A; peribronchial F
♀ 39	78†	—75	MDI	MA	MA	MI	Heart, F; pancreas, A
♂ 40	78	—84	MDI	M	AMI	M	Spleen and testes, A
♂ 41	78	—73	MDI	MDAI	M	MI	Testes and spleen, A

* M indicates metaplasia; D, dilatation of ducts; I, infection; A, atrophy; F, fibrosis; B, bronchitis; P, pneumonia.

† Animal died.

to any conclusions. Two uteri showed marked cornification of the linings with infection. Another uterus showed cornification with marked infiltration by eosinophils in the submucosa.

Male Genitalia: Edema of the testes was seen occasionally. It was present beneath the capsule and extended slightly between the glands.

TABLE 2.—*Pathologic Changes in Various Tissues of the Albino Rat in Early Stages of Vitamin A Deficiency—Continued*

Animal	Duration of Experimental Period, Days	Changes in Weight Last 12-15 Days of Experiment, Gm.	Posterior Part of Tongue	Salivary Glands	Respiratory Tract	Urinary Tract	Other Pathologic Changes
♂ 42	78	—51	ID	MI	AMI	M	Testes, A; spleen, A; peribronchial edema; ducts of pancreas, M
♂ 43	109	—51	.....	....	B	M	Testes, A
♀ 44	63	+11	.....	....	....	..	
♀ 45	63	+ 8	.....	....	P	M	
♀ 46	146	—13	.....	....	....	M	Testes, A; peribronchial infiltration
♂ 47	145	—43	.....	....	MI	..	Testes and spleen, A; peribronchial infiltration
♀ 48	52	+ 4	.....	....	B	M	Liver, F about portal spaces; spleen A
♂ 49	50†	+ 5	.....	....	P	M	Testes and spleen, A; liver, congestion
♂ 50	58	+ 2	.....	....	APB	M	Testes and spleen, A
♂ 51	58	+ 7	.....	....	....	M	Lungs, edema; spleen, A
♂ 52	58	—13	.....	....	P	M	Heart, F; spleen, A; peribronchial infiltration
♂ 53	58	— 4	.....	....	P	M	Testes and spleen, A; heart, F

TABLE 3.—*The Effect of Vitamin A Deficiency on Organ Weights of the Albino Rat*

Organ	Experimental Animals (42)		Control Animals (19)	
	Weight, Gm.	Percentage of Body Weight	Weight, Gm.	Percentage of Body Weight
Adrenal glands	0.0272	0.0185	0.0298	0.0176
Heart	0.8326	0.5478	0.8158	0.4625
Spleen	0.5005	0.3211	0.5733	0.3226
Kidneys	1.6379	1.0660	1.7047	0.9265
Liver	6.1544	4.0741	7.6984	4.3519

In one animal there was extensive edema beneath the basement membrane. Atrophy of the tubules was common, either general or localized, with destruction of parenchymal cells. In one epididymis, the ducts were dilated with pus.

Spleen: Atrophy was usual.

Lymph Nodes: Those in the neck were larger than normal. There was slight hyperplasia, with phagocytic cells in abundance.

Heart: Fibrosis of the heart muscle was noted in two animals. Fragmentation was common, but this was present in the controls.

Estrual Cycle in Early Stages of A Avitaminosis.—The animals when started on the experiment were from 28 to 38 days of age and weighed from 41 to 84 Gm. The estrual cycles were followed daily in twenty pathologic animals and in twelve controls. At the time that the twenty pathologic rats were killed, owing to some early sign of vitamin A deficiency (as indicated by vaginal smear, incipient ophthalmia or cessation of growth), only nine of the females showed the persistence of the cornified stage of the estrual cycle. For instance, females 3 and 7, which were put to death at the first sign of slight ophthalmia, had metaplastic changes, also infection in the posterior portion of the tongue, before growth had ceased, yet these animals had a normal estrual picture. Female 31, which had no ophthalmia but had cessation of growth, metaplasia of the salivary glands and metaplasia with infection of the posterior part of the tongue and of the respiratory and urinary tracts, presented a normal estrual picture. The tongue, in addition, showed dilatation and fibrosis. Females 34 and 35 had incipient signs of ophthalmia and some metaplastic changes but a normal estrual cycle when they were killed, and female 34 was still growing. Female 11 not only had at the termination of the experiment metaplasia of the posterior part of the tongue, of the salivary glands and of the respiratory and urinary tracts, but also had lost considerable weight during the last two weeks of the experiment, and yet had a normal estrual cycle. From these results we conclude that a persistence of the cornified stage of the estrual cycle in the rat is not a positive index to the first signs of vitamin A deficiency, as claimed by Evans and Bishop.[4]

Growth in Early Stages of A Avitaminosis.—Neither is cessation of growth a reliable criterion of the first signs of vitamin A deficiency. It was found that thirty-eight of fifty-three animals, or 71 per cent of the animals deficient in vitamin A, showed metaplastic changes before decline of body weight or complete cessation of growth took place, as evidenced by weight records of the last two weeks of the experimental period. As a matter of fact, twelve of the thirty-eight animals still showed normal growth after manifesting metaplastic changes that were not detected in the controls.

It is interesting to note that female 45, which furnished external signs of incipient ophthalmia for a period of sixteen days before being put to death, was still actually gaining slightly in weight before the termination of the experiment, although having a cleancut case of pneumonia and metaplasia of the urinary tract. Also female 48 had bronchitis before cessation of growth took place, and female 49 died from pneumonia without any external signs of vitamin A deficiency. Male 53 had pneumonia accompanied by an insignificant loss of weight, and female 29 had pneumonia accompanied by metaplasia, atrophy and infection of the respiratory tract, metaplasia and atrophy of the salivary

glands and metaplasia, dilatation and fibrosis of the posterior part of the tongue, without any external signs of vitamin A deficiency.

An examination of table 3, showing the effect of vitamin A deficiency on organ weights, discloses no noteworthy changes in the weight of the adrenal glands, which we found hypertrophied in vitamin B deficiency.[17] There was no actual gain in the weights of the hearts of the pathologic animals, but when the heart weights were considered as percentages of body weights there was apparent a slight hypertrophy. The changes in weights of the kidneys, calculated as percentages of body weights, also indicated some hypertrophy in vitamin A deficiency. The livers showed some atrophy in this avitaminosis.

Summary.—It is clear from an analysis of our data that pathologic changes may take place in tissues as a result of vitamin A deficiency before any definite signs of external symptoms are apparent. We would therefore suggest from our experimental observations that, in vitamin A deficiency, metaplasia of epithelial structures in the respiratory tract of man possibly begins before definite external symptoms are evident, which later may be responsible for the respiratory disturbances, such as are found associated with the A avitaminosis—the common cold, bronchitis and bronchopneumonia.

REPORT OF A CASE OF A AVITAMINOSIS IN A CHILD

One of us (H. S. T.) recently studied the tissues of a boy, 13 months old, who evidently had been suffering from vitamin A deficiency.

The patient was admitted to the Children's Hospital in Little Rock, Ark., on Oct. 15, 1931, because of bilateral ophthalmitis with a left corneal ulcer, 5 mm. in diameter. He died on Oct. 29, 1931, with the clinical diagnosis of bronchopneumonia.

He had been fed breast milk exclusively from a mother who had been starved. He had been suffering undoubtedly from a lack of vitamin A in the diet, for, according to the careful experiments of Macy and others,[18] human milk does not contain a sufficient amount of this vitamin when the mother has not received it in the diet. The child's diet included, however, cod liver oil, as well as other sources of vitamin A, during the fourteen days in the hospital.

An autopsy limited to the neck, thorax and abdomen was made by Dr. A. F. DeGroat. The anatomic diagnosis was as follows: Corneal ulcer with perforation of the left eye; bronchopneumonia (bilateral); acute parenchymatous degeneration of the kidneys, liver and heart; acute splenic hyperplasia; lessened yellow material in the suprarenal cortices; slight emaciation; and hyperplasia of the splenic and mesenteric lymph nodes.

The microscopic examination showed: foci of subacute inflammation in the subpapillary layer of the corium, with occasional erosion of the lower layers of epithelium of the posterior part of the tongue; occasional metaplasia of the lining cells of ducts; occasional metaplasia of the lining cells of ducts of the sublingual

17. Sure, Thatcher and Walker: Arch. Path. **11**:413, 1931.
18. Macy, Outhouse, Graham and Long: J. Biol. Chem. **73**:175, 1927.

and submaxillary glands, with foci of subacute inflammation and destruction of acini in the latter; subacute inflammation of the submucosa of the larynx and trachea, with occasional metaplasia of the lining cells of tracheal ducts; subacute inflammation of the bronchial submucosa; acute bronchitis; bronchopneumonia; slight hyperplasia of the lining of the renal pelvis; congestion of the liver, and acute hyperplasia of the spleen.

There were no noteworthy changes in the heart, aorta, urinary bladder, ureters, intestines and testicles.

Xerophthalmia and keratomalacia in children on a diet deficient in vitamin A have often been reported. One of the latest of these reports is that by Block.[19] Unfortunately autopsies have not been studied to any extent with this point in view. The most convincing autopsy report is that by Wilson and DuBois.[20]

Our case was clinically and pathologically that of a child who had a diet deficient in vitamin A. Although the pathologic observations did not conform exactly to those in our rats, yet it was possible that the vitamin A in the cod liver oil and in the diet after admission to the hospital altered the original changes in the salivary glands and in the posterior part of the tongue. However, enough evidence was present in these tissues to place the lesions in the category of pathologic changes due to a diet deficient in vitamin A.

SUMMARY

Metaplastic changes in the posterior part of the tongue, in the salivary glands, and in the respiratory and urinary tracts were found during early stages of vitamin A deficiency in a large proportion of animals that made normal growth, some of which showed incipient ophthalmia or persistence of the cornified stage of estrum as the only sign of vitamin A deficiency, and others of which showed no external signs of A avitaminosis.

Bronchitis and pneumonia were also found in several animals that still made slight gains in weight before the termination of the experiment.

It is suggested that metaplasia of epithelial structures in the respiratory tract of man may be the precursor of the common cold, bronchitis and bronchopneumonia resulting from vitamin A deficiency, before any other external symptoms are detected by physical diagnosis.

19. Block, C. E.: Am. J. Dis. Child. **42**:263, 1931.
20. Wilson, J. R., and DuBois, R. G.: Am. J. Dis. Child. **26**:432, 1923.

RESISTANCE TO INSULIN

THE RESPONSE TO INSULIN IN RABBITS DURING LEUKOCYTOSIS INDUCED BY SODIUM NUCLEINATE

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The increased dosage of insulin required to lower the blood sugar in many diabetic patients during an acute infection is a phenomenon of considerable theoretical interest for which no satisfactory explanation has yet been found. Infection not only appears to aggravate the diabetic state, causing marked loss of carbohydrate tolerance, but also often alters the response to insulin so that the dosage is out of proportion to the increased blood sugar incident to the infection. However, as Joslin [1] said, "At almost any moment during an infection recovery may begin and the need for insulin suddenly abate," and he warns against the danger of hypoglycemia at such a time. On the other hand, there are some cases recorded in which there is increased response to the usual dose of insulin during infection or gangrene.

When infection is superimposed on the diabetic state, the result is complex. If the response to insulin becomes decreased, how much of this is due to altered tolerance for carbohydrate incident to the infection with consequent greater requirement of insulin, and how much is due to actual inhibition of the action of insulin? The two processes cannot be separated in the diabetic patient. The phenomenon as seen in the diabetic patient might, however, be analyzed and simplified if one had more data on what effect infection per se, in the absence of diabetes, has on carbohydrate metabolism and the response of animals to insulin. There is some clinical evidence of disturbance in carbohydrate metabolism that may be incident to some infections in nondiabetic persons, as manifested by a slight rise in blood sugar values during fasting and by decreased tolerance for dextrose.

Alterations in carbohydrate metabolism occurring during infection might be explained in several ways:

1. Decreased utilization of carbohydrate might result from a depression in the activity of the pancreas. Although there is evidence that infection may cause anatomic injury to the islands of Langerhans, it seems inconceivable that an anatomic injury can account for the change

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1. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928, p. 711.

in response to insulin during infection in diabetic patients, as the restoration to previous conditions when the infection is removed is too rapid for anatomic regeneration to be possible.

2. The altered response to insulin during infection may be due to physiologic factors opposing the effect of insulin, such as a stimulation of the sympathetic nervous system and of the suprarenal and thyroid glands. Experimentally, intravenous injection of bacteria or of bacterial products into rabbits has been found by a number of investigators to cause a temporary elevation of the blood sugar level. In the case of Bacillus coli and B. proteus, the hyperglycemia in rabbits was found to be due to activity of the adrenal and thyroid glands (Geiger and Szirtes,[2] Evans and Zeckwer [3]). It is well known that after thyroidectomy a much smaller dose of insulin will cause convulsions than that which is required before thyroidectomy in the same animal. The antagonism between insulin and the adrenal glands has been demonstrated experimentally by a number of investigators. It is well established that when the blood sugar falls to a dangerously low level after administration of insulin, there is increased glycogenolytic activity. This effect antagonistic to the action of insulin depends not only on the degree of sympathetic and adrenal activity, but on how much glycogen is available for mobilization. Thus, if glycogen is abundant and readily mobilized, convulsions are inhibited. If there is little glycogen to be mobilized, or if mobilization is prevented by removing one adrenal gland and cutting the opposite splanchnic nerve, the animal goes into convulsions with an extremely small dose of insulin.

Reasoning then on this basis, if infection increased glycogenolytic activity, through the sympathetic nervous system, adrenal glands or thyroid gland, at first any insulin injected would be used up by the dextrose derived from hepatic glycogen, but if severe, prolonged infection might exhaust the glycogen store, there would be increased response to insulin if it were given in sufficiently large doses to lead to glycogenolysis. These changes being purely functional, prompt restoration to former conditions after infection has subsided could be more readily understood than if the disturbance in carbohydrate metabolism were due to anatomic injury to the islands of Langerhans. Probably involved in the whole matter is the increased catabolism of body tissues in sepsis.

Lawrence and Buckley [4] studied the response to insulin in rabbits before and after lethal doses of diphtheria toxin, and considered that there was a diminishing response to insulin after diphtheria toxemia was established. Unfortunately, it is hard to evaluate the results, as some

2. Geiger, E., and Szirtes, L.: Klin. Wchnschr. **4**:1912, 1925.
3. Evans, C. L., and Zeckwer, I. T.: Brit. J. Exper. Path. **8**:280, 1927.
4. Lawrence, R. D., and Buckley, O. B.: Brit. J. Exper. Path. **8**:58, 1927.

of the controls that had not received injections of diphtheria toxin showed hyperglycemia after insulin. One of these animals presented a blood sugar of 0.412 per cent three hours after the administration of insulin, with a drop in temperature; another rabbit that had been unaffected by the diphtheria toxin showed a blood sugar of 0.207 per cent in two hours after the administration of insulin and became limp, with a fall in temperature; in a footnote they state that three other rabbits showed similar phenomena. Since the blood was always withdrawn by cardiac puncture, a hematopericardium undoubtedly accounts for the rise in blood sugar and the fall in temperature. In my experience, a slight extravasation of blood into the pericardial sac of the rabbit causes respiratory embarrassment and hyperglycemia of asphyxial type. If this hyperglycemia happened in the controls so frequently, the conclusions do not seem valid. Furthermore, results after diphtheria toxin has been given can scarcely be compared with the pyogenic infections frequently occurring in diabetic patients. Andrews and Schlegel [5] were unable to confirm Lawrence and Buckley's results, while Netzley [6] found insulin less effective when injected at the onset of intoxication by diphtheria toxin. Sweeney [7] found that diphtheria toxemia of rabbits did not cause a change in the action of injected insulin, but caused decreased tolerance of dextrose, and he suggested that the toxemia suppresses endogenous production of insulin.

3. A third possible explanation of the disturbance in carbohydrate metabolism during infection is that there is chemical inactivation of insulin, as by bacterial toxins or the enzymes of leukocytes and tissues.

Rosenthal and Behrendt [8] mixed human pus with insulin and then injected the mixture into rabbits. There was no effect of insulin. If the pus was first heated and then mixed with insulin, the injection resulted in an insulin effect. The insulin was injured by the proteolytic enzymes of the unheated pus, which is to be expected in view of the well known fact that insulin is rendered ineffective when mixed with proteolytic enzymes. They found that rabbit pus had slight effect in comparison with human pus. Similar experiments were carried out by Karelitz, Leader and Cohen,[9] who found that when insulin was incubated with pus from a patient with empyema or with cells of myeloid leukemia or with the plasma of patients with infection, the insulin effect was inhibited, unless the substance was heated before being mixed with insulin. Andrews and Schlegel [5] found that when necrotic material was

5. Andrews, E., and Schlegel, K. W.: Arch. Int. Med. **40**:637, 1927.
6. Netzley, R. E.: Am. J. Dis. Child. **37**:511, 1928.
7. Sweeney, J. S.: Arch. Int. Med. **41**:420, 1928.
8. Rosenthal, F., and Behrendt, R.: Ztschr. f. d. ges. exper. Med. **53**:562, 1926.
9. Karelitz, S.; Leader, S. D., and Cohen, P.: Arch. Int. Med. **45**:690, 1930.

injected simultaneously with insulin into a normal animal, no inhibition of insulin occurred. In this case, there probably had not been time for in vitro destruction of insulin.

Whether such wholesale destruction of insulin could be caused in vivo by the enzymes of circulating leukocytes as occurs when pus and insulin are mixed in vitro is unanswered by these experiments. Perhaps a method that approaches better the actual conditions is that of Depisch and Hasenöhrl,[10] who injected a convulsant dose of insulin after injecting the serum of a diabetic person who was insulin-resistant owing to infection, and found that convulsions did not result. This was controlled by noting the usual effect of insulin when the same dose was injected with the serum of a diabetic person who was responsive to insulin. These experiments indicate that enzymes may be circulating in the blood in sufficient quantities to inhibit injected insulin. However, it is stated that the blood from three other insulin-resistant persons did not give corresponding results.

Karelitz, Leader and Cohen[9] injected typhoid or staphylococcus vaccine into rabbits to simulate the effect of infection, and found that some of the animals showed a moderately decreased insulin effect, and they interpreted this as evidence that some substance chemically inhibits the action of insulin. Harris, Ringer and Lasker[11] incubated cultures of streptococci with insulin, then injected the mixture into mice, and obtained the same effect as with insulin alone. Similarly Andrews and Schlegel,[5] mixing dead staphylococci with insulin, obtained an insulin effect. The explanation probably is that these bacteria have not destroyed the insulin by proteolytic enzymes.

Buckley[12] injected trypsin into rabbits and then studied the response to insulin, and concluded tentatively that injections of trypsin lessen the response to insulin. Here, again, the blood was withdrawn by cardiac punctures, and the effect of this, previously discussed, is manifested in two of the rabbits, for which rather high blood sugar values were recorded before trypsin was injected.

Whether the enzymes of circulating leukocytes may neutralize insulin in vivo is an important point to determine. A number of foreign investigators have been concerned with this problem, and a study has been made of the effect of insulin during leukocytosis induced by sodium nucleinate, with variable results. No data have been found in the literature correlating leukocyte counts of patients with resistance to insulin during infections, and no data have been found of any difference in response to insulin in the rare cases in which diabetes and leukemia

10. Depisch, F., and Hasenöhrl, R.: Ztschr. f. d. ges. exper. Med. **58**:110, 1928.
11. Harris, M. M.; Ringer, A. I., and Lasker, M.: Arch. Path. **4**:546, 1927.
12. Buckley, O. B.: Brit. J. Exper. Path. **12**:13, 1931.

occur in the same patient. Rosenthal and Behrendt [8] studied the reaction to insulin in three nondiabetic patients with infections, but the data show that these patients had no marked leukocytosis. In two of these, patients with empyema, there was a very slight response to insulin, while in the third, a patient with pyonephrosis, a marked lowering of the blood sugar level occurred. It is not known what the response to the same amount of insulin was in the same patients in the absence of infection.

EXPERIMENTAL PROCEDURES

Experiments were carried out in an attempt to study what factors may be involved in the altered response to insulin during acute infection. The problem was narrowed down to the question of whether leukocytosis induced by a chemical agent, such as sodium nucleinate, which has been used by other investigators for similar purposes, rather than by a bacterial agent, modifies the response to insulin in rabbits by chemical or by physiologic antagonisms.

In the first experiments, nonconvulsive doses of insulin were used, but the results showed that the drop in blood sugar from a normal level to a level above the point at which convulsions would occur was so slight and so variable that no clearcut comparison could be made between normal and experimental conditions. Larger doses were therefore used, and convulsions were taken as the criterion for insulin action. Preliminary experiments [13] indicating that leukocytosis may in a certain number of cases inhibit the action of insulin were followed by the more complete experiments reported in this paper.

Since the response of individual rabbits to insulin varies considerably, and varies in the same rabbit at different times, instead of a group of control rabbits being compared with a group of experienced animals, each animal was its own control; that is, the response to insulin was determined one or, more often, several times under standard conditions, then the same animal was given an intravenous injection of sodium nucleinate to produce leukocytosis, and the response to insulin under these conditions was compared with the previous response under normal conditions. In most cases, the animal was allowed to recover from the experimental condition, and then at a later date was again tested for a normal response, in order to reduce the possibility that the animal had changed in response to insulin merely because of often repeated doses.

The intravenous injection of sodium nucleinate in doses of 0.1 Gm. results in transient leukopenia followed by leukocytosis, which persists for many hours. Repeated doses are well tolerated, and leukocytosis induced by this chemical agent is more easily controlled than a bacterial infection and permits a return to normal conditions for comparison. A fast of a number of hours, stated in the table, preceded the injection of insulin. This period was not always exactly the same, but in a herbivorous animal, in which the stomach is full even after a long fast, the period of fast need not be controlled as rigidly as in other animals, as shown by Scott,[14] who found that the maximum precision is obtained in rabbits after about ten hours' inanition, and that the blood sugar remains steady for the following

13. Zeckwer, I. T.: Arch. Path. **9**:1297, 1930.

14. Scott, E. L.: Arch. Int. Med. **43**:393, 1929.

fourteen hours. Injections of insulin were given at appropriate intervals so as to insure that regular feeding was not interfered with between consecutive injections.

Determinations of the preliminary blood sugar levels were made by the Hagedorn and Jensen method, requiring 0.1 cc. of blood, and the occurrence of hypoglycemic convulsions after a small convulsive dose of insulin was taken as the criterion of insulin action. Many of the blood sugar determinations were made by Mr. A. J. Abbott and Mr. Fred W. Van Buskirk, Jr. As soon as the convulsions occurred, dextrose was given intraperitoneally or intravenously to prevent further loss of hepatic glycogen and to save the animal for later experiments. Leukocyte counts were made immediately before the injections of insulin on blood flowing freely from a prick of a vessel of the ear.

The table gives four examples of the results. For the sake of brevity, the results of all the injections of insulin are not recorded, those omitted being results similar to those recorded or the results of injection of insulin in doses far above or far below the approximate minimal convulsive dose.

RESULTS

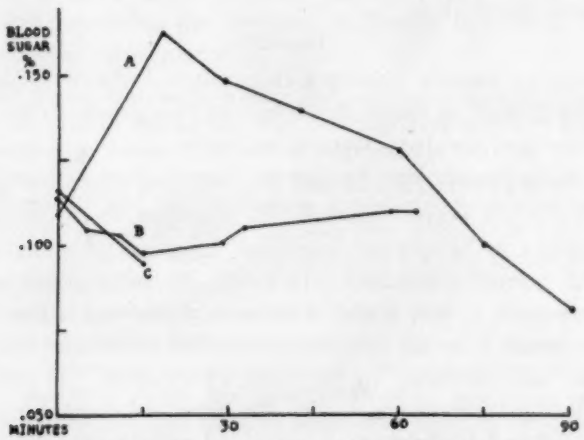
Response to Insulin During Leukocytosis Induced by Injections of Sodium Nucleinate in Intact Rabbits.—In this group twelve intact rabbits were studied, and two effects were noted:

1. In three rabbits (29, 33 and 51), definite inhibition of the action of insulin did not occur. Instead, the response to insulin appeared in most instances to be greater after the injection of sodium nucleinate than under normal conditions. In rabbit 29, when blood sugar values were determined, it was found that twice there was a low preliminary level some hours after the injection of sodium nucleinate and just before the insulin was injected. In the other two rabbits (33 and 51), when sugar determinations were made, the level was not lowered, but in rabbits 31, 38 and 40 there was a low blood sugar level after the injection of sodium nucleinate. This indicated the need of following the blood sugar for a number of hours after injection of sodium nucleinate. Immediately after injecting sodium nucleinate the blood sugar rose; it reached its highest point in about fifteen minutes and dropped to below normal in about two hours, a type of curve suggesting a sudden release of glycogen from the liver by activity of the sympathetic nervous system or of the adrenal glands (chart 1). Twenty-four hours later the blood sugar was either at a normal level or at a lower level. The low blood sugar levels found in certain rabbits occurred only when more than one injection had been given. It is doubtful if a single injection would be sufficient to deplete appreciably the store of glycogen. In two rabbits in which one adrenal gland had been removed and the opposite splanchnic nerve cut, no rise in blood sugar occurred after the injection of sodium nucleinate, but instead a slight drop, proving that when hyperglycemia

results from sodium nucleinate in the intact animal it is because glycogen is discharged from the liver through sympathetic-adrenal activity (chart).

2. Among the other nine rabbits were three (31, 32 and 50) that showed doubtful inhibition of convulsions during leukocytosis. In rabbits 31 and 32, two out of three times in each animal under normal conditions insulin resulted in convulsions, while both times after the injection of sodium nucleinate, convulsions did not occur with the same dosage. Rabbit 50 showed inhibition once and failed to show it a second time.

The other six (35, 37, 38, 49, 53 and 54) showed apparent inhibition of convulsions, provided the leukocyte count was high after the injection of sodium nucleinate, and provided the dose of insulin was not much



Blood sugar values after intravenous injection of 0.1 Gm. of sodium nucleinate: *A*, in intact rabbit 37; *B*, in rabbit 39 after right adrenal gland had been excised and left splanchnic nerve cut; *C*, in rabbit 49 after left adrenal gland had been excised and right splanchnic nerve cut.

above the minimal convulsive dose. In those cases in this group (31 and 38) in which blood sugar values were low after the injection of sodium nucleinate, inhibition occurred in spite of the low blood sugar levels at the time of the injection of insulin. It has been shown that each injection of sodium nucleinate apparently mobilizes glycogen from the liver, and that if these injections are repeated at short intervals the animal has less glycogen available for counteracting the effect of insulin, and yet, in spite of this loss of glycogen, insulin convulsions may be prevented. Blood sugar values taken at the time of convulsions were in most instances lower than those taken when convulsions were inhibited, the blood in the latter case being obtained at the same interval

Rabbit	Date	Body Weight, Kg.	Hours of Fast	Experimental Condition	Blood Sugar Percentage Before Injection of Insulin	Units of Insulin Injected	White Blood Cell Count	Convulsions	Time of Convulsions, Min. After Injection of Insulin	Comment
R 29	5/10/29	1.84	22	Normal	0.111	2	4,800	+	85	
	6/ 5/29	....	16	17 hr. after 1 Gm. sodium nucleinate	0.073	2	256,000	+	75	No inhibition
	6/11/29	1.64	21	20 hr. after 0.1 Gm. sodium nucleinate	.....	2	91,000	+	70	Nucleinate increased effectiveness of insulin
	6/28/29	....	24	Normal	0.111	1	6,100	0	...	
	7/ 9/29	1.82	24	18 hr. after 0.1 Gm. sodium nucleinate	0.063-0.086	1	21,000	+	90	
R 38	10/29/29	....	21	Normal	.....	1	14,000	+	110	Before operation, inhibition with 1 unit when leukocytes were high, but not with 2 units
	11/12/29	2.14	17	Normal	0.108	0.5	6,000	0	...	
	11/16/29	....	19	19 hr. after 0.1 Gm. sodium nucleinate	0.091	2	21,900	+	90	
	11/19/29	2.04	20	20 hr. after 0.1 Gm. sodium nucleinate	0.124	1	13,400	+	80	
	11/26/29	2.00	18	18 hr. after 0.1 Gm. sodium nucleinate	0.083	1	20,600	0	...	
	12/ 3/29	2.06	20	20 hr. after 0.1 Gm. sodium nucleinate	0.107	1	27,000	0	...	
	12/ 5/29	....	18	18 hr. after 0.1 Gm. sodium nucleinate	.....	1	11,800	+	115	
	12/19/29	2.24	..	Left adrenal excised, righ splanchnic nerve cut						
	12/31/29	2.16	20	12 days after operation	0.101	0.5	16,400	+	80	After operation, inhibition in spite of low blood sugar
	1/ 3/30	1.94	17	17 hr. after 0.18 Gm. sodium nucleinate	0.066	0.5	77,800	0	...	
R 49	9/24/30	2.00	21	Normal	0.103	2	13,000	+	105	
	9/30/30	1.94	21	Normal	0,116	2	15,000	+	120	
	10/22/30	2.14	20	21 hr. after 0.15 Gm. sodium nucleinate	0.113	2	22,600	+	140	
	11/ 5/30	....	21	21 hr. after 0.15 Gm. sodium nucleinate	0.115	2	74,000	0	...	Inhibition, when leukocytes were high, with dose larger than minimal convulsive
	11/11/30	2.40	20	Normal	0.076	2	19,400	+	105	
	11/25/30	....	19	19 hr. after 0.15 Gm. sodium nucleinate	0.100	2	56,800	0	...	
	12/ 5/30	2.62	19	Normal	.....	2	15,700	+	180	
	12/10/30	2.60	16	Normal	0.094	2.25	12,400	+	150	
	12/11/30	2.60	16	16 hr. after 0.15 Gm. sodium nucleinate	.....	2.25	52,000	0	...	
R 67	5/ 5/31	....	..	Thyroidectomy						
	6/17/31	2.04	..	Normal	.....	2	.....	0	...	After thyroidectomy, inhibition with dose larger than minimal convulsive
	6/26/31	2.08	18	Normal	.....	2.5	.....	+	165	
	6/30/31	2.04	18	18 hr. after 0.1 Gm. sodium nucleinate	.....	2.75	15,000	0	...	
	7/ 9/31	2.06	20	18 hr. after 0.1 Gm. sodium nucleinate	0.090	3	110,000	0	...	
	7/11/31	1.98	17	Normal	0.115	2.75	9,800	+	135	

of time after the injection of insulin as that at which the rabbit had previously shown convulsions.

This inhibition of insulin convulsions may have two explanations: 1. Glycogenolytic activity may be increased by sodium nucleinate even after the initial glycogenolysis, thus offering a physiologic antagonism to the hypoglycemic effect of insulin. 2. The circulating leukocytes may inactivate insulin, probably by their proteolytic enzymes. To gain data supporting or controverting the postulates just outlined, further experiments were carried out.

Effect of Sodium Nucleinate on Action of Insulin at Time When Leukocytosis Fails to Occur.—When sodium nucleinate is repeatedly injected, the bone marrow becomes more or less depleted of myeloid elements, so that a marked rise in circulating leukocytes no longer occurs (Doan, Zerfas, Warren and Ames;[15] Zeckwer[16]). If the response to insulin after the injection of sodium nucleinate in such an animal with no leukocytosis is compared with that in the same animal under normal conditions and with that after previous injections of sodium nucleinate from which marked leukocytosis resulted, any alteration in the response might be due to the numbers of leukocytes and not to the sodium nucleinate per se.

Rabbits 37 and 38 showed that apparent inhibition of the action of insulin occurred when the leukocytosis was marked, but inhibition failed to occur when leukocytosis was not present (see table). In rabbit 37, the leukocyte count was only 7,400 seventeen hours after the third injection of sodium nucleinate, and this time 2 units caused convulsions, while a similar dose had failed to cause convulsions on two previous occasions when the leukocyte counts were 22,800 and 32,000. In rabbit 38, when the leukocyte count after a repeated injection of sodium nucleinate was only 13,000, insulin convulsions were not inhibited, but after the bone marrow was rested, subsequent injections of sodium nucleinate resulting in a leukocytosis of 20,600 and 27,000 inhibited the same dose of insulin, while after a still later injection of sodium nucleinate resulting in a leukocyte count of only 11,800, convulsions occurred.

Other rabbits showed the same phenomenon. For instance, rabbit 49 showed inhibition of convulsions when the leukocyte counts were very high, but not when leukocytosis was only moderate.

These results appeared to be evidence that when the action of insulin had been inhibited, this was due to the leukocytes, not to the effect of sodium nucleinate per se. Nevertheless, since sodium nucleinate had

15. Doan, C. A.; Zerfas, L. G.; Warren, S., and Ames, O.: J. Exper. Med. **47**:403, 1928.

16. Zeckwer, I. T.: Arch. Path. **7**:1012, 1929.

been definitely shown to mobilize glycogen, both factors might be concerned. Accordingly, it now became necessary to see what effect eliminating the physiologic factors responsible for glycogenolysis had on the response to insulin after the injection of sodium nucleinate.

Effect on Response to Insulin During Sodium Nucleinate Leukocytosis of Inhibiting Glycogenolysis by Removal of One Adrenal Gland and Cutting of Opposite Splanchnic Nerve.—In three rabbits one adrenal gland was removed and the opposite splanchnic nerve cut under aseptic conditions, and recovery from the immediate effect of the operation was permitted by a rest of a number of days before the response to insulin was studied. It has been shown by a number of investigators that in such animals the minimal convulsive dose of insulin is much smaller than in intact animals, as the action of insulin is opposed by less glycogenolysis. When a small convulsive dosage was determined after operation, sodium nucleinate was injected and the response to insulin tested, as before, in these animals that had been operated on.

In such animals any effect that sodium nucleinate might have in mobilizing glycogen and in that way inhibiting insulin was prevented, as previous experience (Evans and Zeckwer [3]) had convinced us that such a procedure was functionally effective in preventing glycogenolysis, in accordance with the findings of a number of previous workers. If any inhibition of the action of insulin should then occur, it would be due to the leukocytosis alone.

A functionally successful operation in these animals was tested in several ways: 1. A series of blood sugar determinations was carried out immediately after the injection of sodium nucleinate, and it was found that the hyperglycemia that occurs in the intact animal no longer occurred, but, instead, a fall. Rabbits 39 and 40 were tested this way. 2. The minimal convulsive dose of insulin before operation was compared with that after operation, and it was found that a much smaller dose was effective after operation (rabbits 38 and 39). There was additional evidence in the manner in which the animals reacted after convulsions occurred. In the normal rabbit, intraperitoneal injection of dextrose resulted in an almost instantaneous recovery from convulsions, the animal quickly jumping to its feet and running away as though nothing had happened. The animals operated on were severely prostrated and showed a slow recovery after receiving dextrose, as one would expect if the compensatory release of glycogen in emergency could no longer occur.

The results were as follows: In rabbit 39, seven days after operation, one-half unit of insulin resulted in convulsions. Six days later sodium nucleinate was injected, but the leukocyte count was only 6,000 when insulin was injected, and the injection of the insulin again resulted in

convulsions. Fifteen days later a larger dose of sodium nucleinate was given, resulting in a leukocytosis of 28,000, and with the same dose of insulin convulsions were prevented. After an interval of a number of days, insulin in the same dose again caused convulsions when the level of the leukocytes was low.

In rabbit 40, inhibition of the action of 1 unit of insulin was not obtained after operation during leukocytosis. This rabbit had not been tested for inhibition before operation.

In rabbit 38, in which before operation inhibition had been shown, after operation one-half unit caused convulsions, but when leukocytosis was produced by sodium nucleinate, convulsions were inhibited.

In rabbit 41, both splanchnic nerves had been cut, but neither adrenal gland had been removed. One unit of insulin caused convulsions before sodium nucleinate was injected, but failed to cause convulsions during the leukocytosis following the injection of sodium nucleinate.

It was concluded from these experiments that, since inhibition of convulsions could occur in animals in which glycogenolysis was prevented by operation, the inhibition of convulsions was not because sodium nucleinate favored a compensating glycogenolysis.

Effect of Thyroidectomy on Response to Insulin During Sodium Nucleinate Leukocytosis.—In view of the influence of the thyroid gland on glycogenolysis, discussed in previous work,[17] three thyroidectomized rabbits were studied. Rabbit 54 had shown apparent inhibition of insulin convulsions before thyroidectomy, and after thyroidectomy it showed inhibition during sodium nucleinate leukocytosis with the previous convulsive dose, but not with a dose larger than that. Rabbits 67 and 69, the response of which to insulin had not been tested before thyroidectomy, showed inhibition after thyroidectomy with doses one-half unit higher than the previous convulsive dose, provided the leukocyte count was high.

COMMENT

One possible source of error must always be considered in experiments of this type, and that is the fluctuations in response to insulin which rabbits show under standard conditions. For instance, a rabbit may tolerate without convulsions ascending doses of insulin and finally succumb to, let us say, 2½ units. Having once had convulsions, it may be more sensitive, and fits may occur with 2 or 1½ units. This spontaneous fluctuation is commonly neglected in many experiments having to do with the effect of insulin in rabbits reported in the literature. It was for this reason that the rabbits were studied under normal conditions, then during leukocytosis, then again under normal

17. Zeckwer, I. T.: Am. J. Path. **7**:548, 1931.

conditions, and then, when possible, again during leukocytosis, in order to reduce as far as possible the likelihood that the results merely coincided with spontaneous fluctuations in response to insulin. However, all possibility that the results noted were influenced by spontaneous fluctuations cannot be ruled out.

These experiments, then, give suggestive but not conclusive evidence that the convulsions following injection of insulin in rabbits may in a certain number of cases be inhibited during leukocytosis induced by sodium nucleinate, but the inconstancy of the results makes definite conclusions impossible. Although after the injection of sodium nucleinate many factors other than leukocytosis may enter into the picture, such as changes in the metabolic rate, yet leukocytosis would seem to be the important factor, as the apparent inhibition, when it occurs, is roughly proportional to the degree of leukocytosis. Since leukocytes destroy insulin in vitro, it seems possible that the enzymes of circulating leukocytes may destroy insulin in vivo.

These experiments throw no clear light on the resistance to insulin in diabetic patients with infections. The apparent inhibition, when obtained in these experiments, was only slight in comparison with the resistance shown in man. However, the proteolytic activity of rabbit leukocytes is much less than that of human leukocytes. It would therefore be of considerable interest to have data on leukocyte counts of patients showing resistance to insulin during acute infections. In man, if leukocytic enzymes play a rôle in this resistance to insulin, there are probably other factors as well.

The use of convulsive doses makes the results more concrete than when a comparison is made of the falls in the blood sugar after nonconvulsive doses. The results with a convulsive dose, however, cannot be compared with the effects of the dosage used in diabetic patients. The use of convulsive doses is a test of the glycogen store, and of the animal's ability to mobilize this store when a dangerous level of blood sugar is reached, while with the dosage of insulin properly used in man, glycogenolysis probably does not occur.

These observations apply only to rabbits. Other animals may behave differently. For instance, the injection of "coli toxin" (Geiger[18]) caused hyperglycemia in rabbits and hypoglycemia in dogs. In studies now in progress, in the one depancreatized dog so far studied, bacterial infection lessened the drop of blood sugar with a small, nonconvulsive dose of insulin, but during leukocytosis of the same degree induced by sodium nucleinate the same dose of insulin was not inhibited. Since so much of the experimental work on insulin has been done on rabbits,

18. Geiger, E.: Arch. f. exper. Path. u. Pharmakol. **121**:67, 1927.

the present experiments are reported in spite of the fact that there is no justification for applying these results to the problem of the response to insulin in other animals or in man.

SUMMARY

Seventeen rabbits were studied for the response to insulin during leukocytosis induced by intravenous injection of sodium nucleinate. The results were variable. In three of twelve intact animals, no inhibition of insulin convulsions occurred during leukocytosis; three showed doubtful alterations in response, and six showed apparent inhibition of insulin convulsions, provided that there was a high degree of leukocytosis, and provided that a small convulsive dose of insulin was used; but the possibility of spontaneous fluctuation in the response to insulin cannot be ruled out, although the experimental methods employed reduced this possibility. Apparent inhibition of insulin convulsions after injections of sodium nucleinate may occur after glycogenolytic activity is reduced by (1) removing one adrenal gland and cutting the opposite splanchnic nerve (two of three rabbits), and by (2) thyroidectomy (all of three rabbits).

Sodium nucleinate injected intravenously causes an immediate hyperglycemia, which is due to glycogenolysis, for it is prevented by previous removal of one adrenal gland and cutting of the opposite splanchnic nerve.

These results do not elucidate the problem of the altered response to insulin in diabetic patients with acute infection, for reasons given in the text.

General Review

THE ORIGIN AND ANTIQUITY OF SYPHILIS: THE EVIDENCE FROM DISEASED BONES

A REVIEW, WITH SOME NEW MATERIAL FROM AMERICA

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Evidence for the existence of syphilis in ancient times may conceivably be derived from written documents or from pictures made by artists of the lesions of the disease or from human remains showing its effects. In the last case, bones must be the principal, if not the only, structures available for study. In this article, I propose reviewing all the ancient bones alleged to be syphilitic of which I can find descriptions in the literature. For the controversy over the testimony of ancient documents, begun four centuries ago, still goes on, and portrayals of disease by ancient artists are few and indecisive. But the industry of archeologists in recent years has brought to light a wealth of material that makes chronology more exact, and that includes some important skeletal remains. I am therefore able to describe some specimens not previously reported.

THE ARCHEOLOGIC PROBLEM

It has often been stated that, for the purposes of such an inquiry as this, one must have proof that a bone is ancient and that it is syphilitic. It is owing to a difference of opinion as to what constitutes proof that the controversy continues.

Now if one could open an intact tomb, inscribed 1000 A.D. or the equivalent of 1000 B.C., containing a skeleton that all pathologists agreed must be syphilitic and could be nothing else, that would be convincing; almost too convincing.

Most of the royal tombs in Egypt were plundered and the mummies in them more or less disturbed. The tomb of King Tutankhamen was the exception that made its discovery famous (Smith and W. R. Dawson). Graves in ancient Greece were robbed or used for burials by later peoples (intrusive burials). The same practice was prevalent among many peoples and in many parts of the world, both in ancient and in modern times.

Some of the most famous of early human remains were found as scattered fragments no longer in their original position. Mr. Charles Dawson recovered parts of the Piltdown skull from spoil heaps where they had been thrown by workmen; other parts were taken from the gravel pit in their original position, considerable times intervening between the different finds. The Neandertal skull and bones were dug out by laborers from a cave and thrown aside, to be recovered later in part by Dr. Fuhlrott. The Gibraltar skull lay for several years in the museum of the Royal College of Surgeons, unhonored and unnoticed; its history was defective, and apparently no record was preserved of the precise circumstances under which it was found. Nevertheless, no archeologist has seemed to doubt the validity of any of these priceless specimens (Hrdlicka, 1914; MacCurdy, 1924).

An investigator working in a period when, or in a region where, there was no written language must enjoy a comfortable sense of security in dating his find if he can demonstrate successive strata of later dates lying above it; as when he discovers neolithic material overlaid by material characteristic of the cultures of the Bronze Age and of historic times. Such sites occur in western Europe. But in many cases there is no such stratification, and he calls his find neolithic because it contains objects that in other places have been proved by stratification to be characteristic of neolithic culture, as polished stone implements, exquisitely flaked flint tools, pottery and certain styles of ornaments; at the same time, it must not contain objects characteristic of later cultures. The plan is the same as that used by geologists when they determine the age of an outcrop of rock by the fossils that it contains. The dates of a large part of the objects displayed in museums of archeology are based on such evidence. All the specimens of bones alleged to be prehistoric and also syphilitic are dated by similar evidence. None of them is accompanied by testimony of any written language; with none of them is there any important assistance from stratified deposits overlying them.[1] Their antiquity is inferred from the type of burial and from the associated pottery, implements and ornaments, and from the absence of objects of later periods. The circumstances surrounding each of the alleged cases and the validity of the evidence are considered hereafter separately. As in criminal trials, a sufficient number of probabilities, all pointing in one direction, may make a powerful case.

Most of the specimens of bones supposed to be ancient and syphilitic reported in recent years have been found in America, so that a brief discussion of the peculiar features presented by American archeology will be appropriate at this point.

In an important paper on prehistoric syphilis by Virchow in 1896, which has often been quoted, it was pointed out that the American Indians continued to use the implements and ornaments of their native culture long after the arrival of the white race. A grave containing the objects characteristic of Indian culture and no objects derived from the whites was not necessarily ancient. Also, those examples of stratification that were quite frequent in Europe were rare in both North and South America.

However, much progress has been made since 1896. Archeologists have been active in studying American problems. One can now be certain in many cases that cultural material and bones are pre-Columbian.

It seems that the Indians of practically the whole of North and South America had a neolithic culture; in Mexico, Central America and Peru, bronze was beginning to be used, but its use was not general.

1. The specimens from Pecos, N. M., may be an exception.

The degree of development of this neolithic culture varies immensely in different parts of America, and may sometimes be used roughly in dating ancient remains. A simple illustration from the state of New York serves as an example.

The first white explorers found most of what is now the state of New York occupied by the Iroquois family of Indians, but even in the middle of the Iroquois region there were clear evidences of an earlier occupation by people having the culture characteristic of Algonkian Indians (Parker). An Algonkian grave occurring in the Iroquois area therefore antedated the arrival of white men.[2]

In the Ohio and Mississippi valleys were the famous works of the Indians called Mound Builders. Most of the mounds were ancient and prehistoric, but some of them were erected by modern Indians. Some contained objects obtained from white men. A relic coming from one of the mounds was not necessarily prehistoric. Certain bones, strongly suspected of being syphilitic, were derived from burial grounds of the Mound Builders.

Archeologists in this field have gone far toward classifying the cultures of the mounds. For instance, that found in the Hopewell group of mounds is a well defined, ancient and prehistoric culture recognizable over a wide area (Mills, Shetrone). Two other cultures, the Adena and Fort Ancient cultures, also appear to have been prehistoric. Furthermore, Shetrone [3] expressed the belief that only a small number of mounds have been built during the historic period, although intrusive burials, recognizable to an expert as such, are not infrequent on the surfaces of these mounds.

The Indians of New Mexico and the adjoining states built impressive structures of stone, often high up under overhanging cliffs (Cliff Dwellers). In open places, they erected the great communal dwellings, like the modern apartment house, called pueblos (the Indians are also called Pueblos). It has been shown that the Pueblos were preceded by a people known as Basket Makers, who had a primitive culture and to whom stone houses and pottery were unknown. Through the efforts of a large number of archeologists,[4] a succession of cultures has been

2. Dr. Parker recently encountered a curious and interesting find in excavating an Iroquois grave in the Cayuga Lake region; the grave contained a coin of the Roman colony in Egypt. The coin, of course, indicated that the burial was modern and not ancient, and that the Indian obtained it from some European missionary or trader.

3. I have been fortunate, as an amateur, in being able to watch Shetrone's technic in the field. As Wissler put it, Shetrone "dissects" a mound in the way that a pathologist dissects a body.

4. The well known and honored American pathologist, T. Mitchell Prudden, who was also an enthusiastic archeologist, was prominent in helping to solve the puzzles presented by the ruins of the Southwest.

discovered: Basket Maker, post-Basket Maker, pre-Pueblo and finally Pueblo. Among the Pueblos, the making of pottery reached a high state of development. Furthermore, styles in pottery changed from time to time so as to indicate a series of subdivisions of Pueblo cultures down to the arrival of the Spaniards (1640) and the present day. It may be noted that the skulls of the Basket Makers were generally long and those of the later Pueblos generally broad. These studies make it possible to give relative dates to many burials with a close approach to certainty (Kidder).

Through the brilliant researches of Douglass, and with the use of his "tree ring" method, it now appears possible to assign exact dates to some of the pueblos. It is stated that one timber at Cliff Palace, Mesa Verde, in Colorado, was cut in 1073 A.D.; others from Pueblo Bonito in Chaco Canyon, New Mexico, were cut in 919 and 1130 A.D. (Douglass, Judd).

The age of these prehistoric ruins seems to be not quite so great as has been supposed. Some of the most important ancient bones that in all reasonable probability are syphilitic come from the Pueblo area.

In Mexico and Central America one encounters the only parts of the American continent where a native written language developed. Through the excavations and studies of recent years much progress has been made in deciphering the Central American hieroglyphics, particularly those of the calendar. A basis for dating relics is, or soon will be, available. Up to this time, little skeletal material bearing on the subject of ancient syphilis has been secured from this region. It must be regarded as a most promising field for future work. However, many bodies were destroyed, owing to the practice of cremation.

Ancient Peru, for an American Indian community, had a large population. The methods of burial and the dry climate and soil have preserved for us an enormous number of skeletons and mummies. The origin and succession of cultures in Peru are matters about which there is much controversy (Kroeber, 1926 and 1930). However, it is usually possible to distinguish remains of the early periods from those of the Inca period. Tradition indicates that the Inca period began about 1200 A.D. Some of the most important evidence for ancient syphilis has been assigned by its discoverers to the pre-Inca period, and it would therefore be pre-Columbian.

Those who believe that historical evidence shows that syphilis originated in America claim that it was conveyed to Spain by sailors of Columbus, who became infected in the island of Haiti. One might expect evidence in the form of diseased bones to exist in Haiti or Cuba or the adjacent islands. There are several difficulties in the way of producing such evidence. Comparatively little archeologic exploration has been done in these islands. The conditions of burial and of climate are not favorable to the preservation of human remains. The

native Indians have been replaced, particularly in Haiti, by a population of Negroes or persons of mixed bloods. Yaws and probably syphilis are prevalent in Haiti. Any syphilitic bones discovered would need to be subjected to the closest scrutiny to determine their antiquity and to exclude the possibility of a recent burial. However, bones that are in all probability syphilitic and that are probably pre-Columbian have been uncovered in Florida (cases of C. B. Moore and Lamb, described hereafter), and Florida is near to Cuba and no great distance from Haiti.

THE PROBLEM OF DIAGNOSING SYPHILIS IN DRIED BONES

For the purposes of this investigation I have devoted considerable time to obtaining a rudimentary knowledge of archeology in the field, and to study of bones affected by syphilis, particularly skulls. I have examined such skulls in London, Paris, Amsterdam, Leyden, Berlin, Leipzic, Munich, Prague, Vienna, Zurich, Boston, Philadelphia and Washington, to mention only museums having fifteen or more skulls labeled syphilitic. I have notes on more than five hundred modern skulls with this diagnosis. The list of cities given is not without significance, for it enables one to say that there seems to be no difference of opinion as to what constitutes a typical syphilitic skull. Not all the skulls labeled syphilitic are perfectly typical; I should estimate that fewer than half of them are, but I should think the perfectly typical syphilitic skull, to be described hereafter, a more certain criterion for diagnosis than a Wassermann reaction of four plus or an aneurysm of the aorta. With long bones the case is different; however, with the assistance of the x-rays and of sections examined under the microscope, a high degree of probability in the diagnosis may be obtained with some long bones.

DESCRIPTION OF SYPHILIS OF BONE

Except in osteochondritis syphilitica of infants, the bones are usually involved late in the course of syphilis. Two principal forms of syphilis of bone are recognized; gummatous and diffuse, or nongummatous. As the gummatous form is more important in connection with the skull and the diffuse form in connection with the long bones, they will be discussed under those headings.[5]

The Syphilitic Skull.—The type of skull that is most characteristic of syphilis is that produced by widespread gummatous inflammation of the periosteum, frequently with localized gummatous nodules. The gummatous periostitis is accompanied by a certain amount of osteitis. It leads to destruction of bone and simultaneously or later there is new formation

5. I have avoided the use of the adjectives specific and nonspecific in this connection, as they seem to me misleading. They are just as appropriate for any other infection as they are for syphilis.

of the bone at the edges of the parts affected. An unevenness or irregularity of the surface of the skull results that is peculiar and distinctive. English books sometimes speak of it as appearing "worm eaten." Erosions bordered by new bone may be present where there were gummas, partly healed. As Virchow stated it, the scars remaining after a gummatous peripheral osteitis are most characteristic; there is deficiency of new formation in the middle with excess at the outer parts. Such scars produce jagged, linear, not rarely stellate depressions, with the most marked defect in the middle, and with smooth, rounded and elevated edges. Virchow revived the term "caries sicca," used by an earlier author, Bertrandi, for this process; that is, caries not accompanied by the pus that goes with acute osteomyelitis and periostitis (fig. 1).

The alterations produced by syphilis frequently affect a large part of the outer surface of the calvaria; the inner surface is rarely involved. They often begin on the frontal bone, but not always. The skull may be abnormally heavy, but is not necessarily so. Gummas may erode so deeply as to cause perforation. Large sequestrums are sometimes formed. Such skulls seem to be less common in congenital than in acquired syphilis (M. B. Schmidt).

The characteristic syphilitic skull used to be found at autopsies in hospitals more frequently than it is now. The same is true of gummas of the viscera, which, all reports indicate, are much rarer than they were thirty or more years ago. This is probably the result of better diagnosis and treatment, though some observers believe that the virulence of the organism that causes syphilis has diminished, speaking only of syphilis as it is now seen in the white race.

Those syphilitic skulls that I have referred to as being not characteristic show various thickenings, protuberances, scars, defects and sometimes necrosis without healing. If there were no other evidence of syphilis present, a diagnosis would be impossible. Some of these cases undoubtedly result from the diffuse, nongummatous form of syphilitic periostitis. The latter produces thickening of the outer surface of the skull, which may be either rough or smooth, and which has no feature that I know of distinguishing it from thickening produced by other causes of chronic periostitis.

Late syphilis is well known to involve the nasal region or hard palate in a considerable proportion of cases. It usually begins as an ulceration of the mucosa that extends into the bone. As the nasal region is often involved in lupus, in yaws (frambesia) and in tropical leishmaniasis, particular care must be exercised in respect to ancient skulls in which the nasal region is the principal part involved. Cases of this kind will appear in some of the material to be discussed farther on.

The notched teeth of congenital syphilis (Hutchinson's teeth) might help establish the diagnosis of syphilis, though not by themselves entirely diagnostic.

In a personal communication, Sir Arthur Keith informed me that the Museum of the Royal College of Surgeons, London, had recently

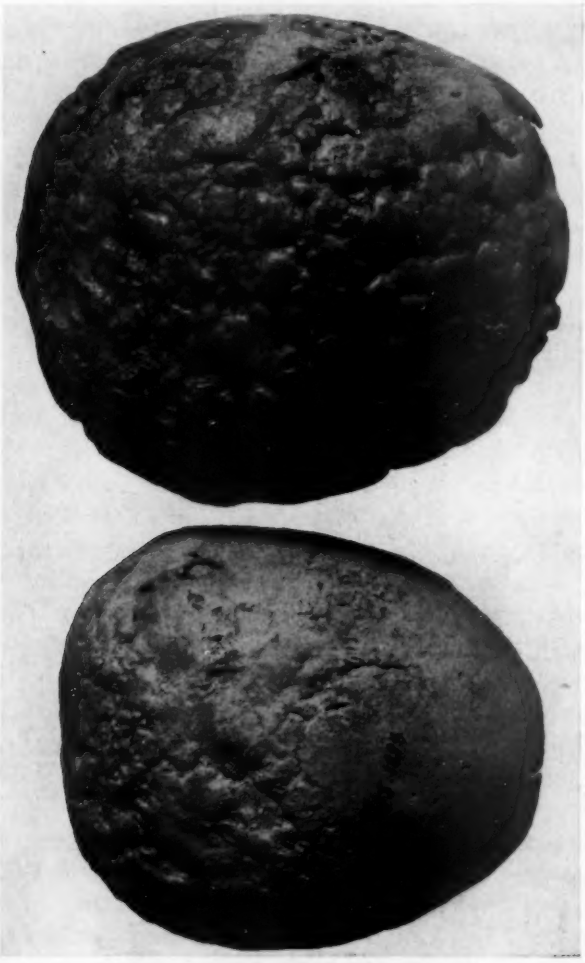

Fig. 1.—Typical syphilis of the skull, of severe type—"caries sicca." The specimens are in the museum of the Rudolf Virchow Hospital (Charité), Berlin; the upper skull is 18802. The photograph for this paper was made by E. Engelener, Berlin, through the courtesy of Professor Lubarsch. (Original photograph.)

acquired from the Society Islands a skull with lesions resembling those of syphilis, but attributed to yaws; the diagnosis of yaws and the exclusion of syphilis would need to be established to a certainty if this

unusual specimen is to be accepted. Osteomyelitis with periostitis apparently does not produce alterations on the skull comparable to those seen in typical cases of syphilis, and I do not know of any such specimen. Tuberculosis may produce destruction of bone, but there is not usually any noteworthy formation of new bone. Professor Tendeloo, of Leyden, called my attention to a skull in his collection from a case of leontiasis ossea in which the highly irregular upper surface of the cranium considerably resembled that seen in healed gummatous periostitis, but the characteristic stellate scarring was lacking, and the enormous thickening of the skull, with the other features of the case, would make confusion most improbable. Several writers have described as syphilis in ancient skulls what appear to me to be examples of symmetrical osteoporosis of the cranium, a disease that was common in some ancient races (Williams, 1929). Lancereaux suggested that leprosy may have produced alterations on the surface of ancient skulls similar to those of syphilis; little information seems available on this aspect of the subject. Leprosy might need to be considered in the case of ancient bones from Europe, Asia and Africa; there is no evidence that it existed in America prior to the discovery by Columbus. Erosion by water and substances dissolved in it, by roots and by rodent animals should not lead to errors on the part of those accustomed to the appearance of ancient bones.

Syphilitic Long Bones.—The gummatous form may occur as in the case of the skull, with destruction and new growth of bone, healing and scar formation. It may affect the interior of the bone, but more often it occurs peripherally. The epiphyses and joints are occasionally involved. It has frequently been noticed that bones that are exposed to injury, such as the top of the skull, the tibia and the clavicle, are likely to be affected, injury determining the location of a gumma. So many conditions produce localized destruction of bone with subsequent thickening and formation of new bone that the diagnosis of this form of syphilis in a single dried bone without its clinical history would be dubious; the involvement of several bones would make a diagnosis of syphilis more plausible. In the case of long bones, few observers lay much stress on the stellate scars described by Virchow as characteristic of syphilis, although such scars are of great importance in the skull. Large areas of necrosis, leading to the formation of sequestrums, may occur; they may be due to secondary infection. Such sequestrums are less frequent in syphilis than in osteomyelitis and tuberculosis. In sections of fresh preparations, the histologic picture of gummatous granulation tissue is present (fig. 6*A*). Spirochetes are said to be rarely demonstrable.

The diffuse, nongummatous form of syphilis of bone has been described especially by German writers. It is often encountered in long bones, and several bones are likely to be involved. This form of syphilis, or something much like it, is largely responsible for the difficulties in diagnosis encountered in ancient dried long bones.

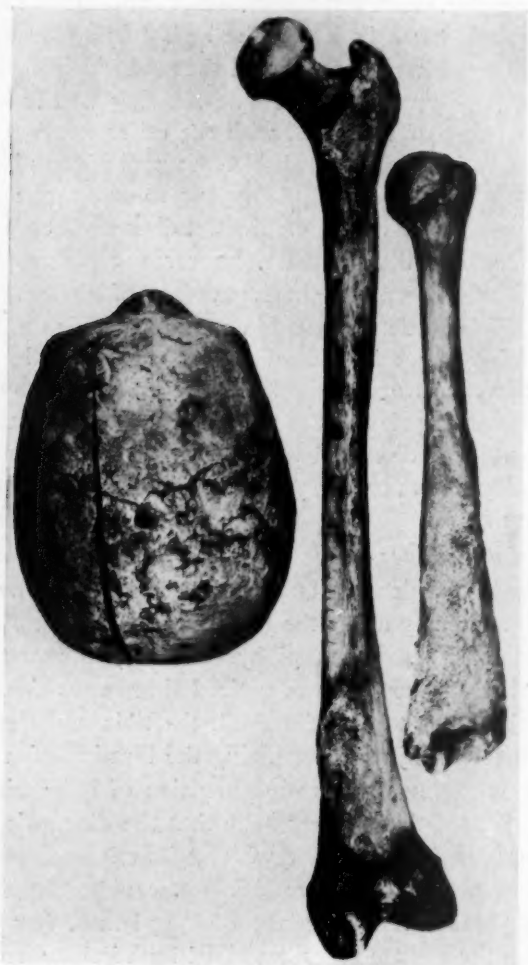

Fig. 2.—The skull and bones of a prostitute, Army Medical Museum, Washington, D. C., no. 6414. The photograph and roentgenogram were furnished by Major George W. Callender. The long bones appear to show both gummatous and diffuse syphilis of bone.

In fresh specimens of this diffuse type an osteoperiostitis is found the histologic appearances of which are said to have nothing characteristic of syphilis. However, the gummatous and the diffuse form may occur

in one and the same bone (figs. 2 and 3). Some observers attribute this periostitis to toxins, but in view of the uncertainty in regard to the pathogenesis of other late syphilitic lesions it is safest to maintain an attitude of reserve in respect to the diffuse periostitis, although the term is useful in classification.

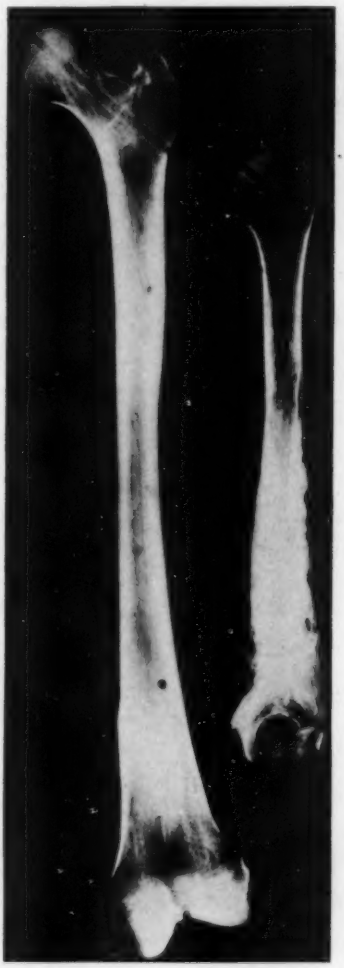

Fig. 3.—A roentgenogram of the long bones shown in figure 2.

The diffuse form of bone syphilis affects the shapes of long bones. Enlargement occurs from new growth of bone beneath the periosteum. The outer surface may be nearly smooth or rough, sometimes extremely rough, suggesting a mixture of the gummatous with the diffuse type. There may be considerable osteophytic growth. The areas of thickening with smooth surfaces may show many small openings for the trans-

mission of blood vessels and often longitudinal grooves. The anterior border of the tibia is a frequent location for such new growths, and a saber-shaped tibia may result, but this is no longer regarded as distinctive of syphilis. Osteitis may occur along with the periostitis, producing new bone that leads to narrowing of the medullary canal;

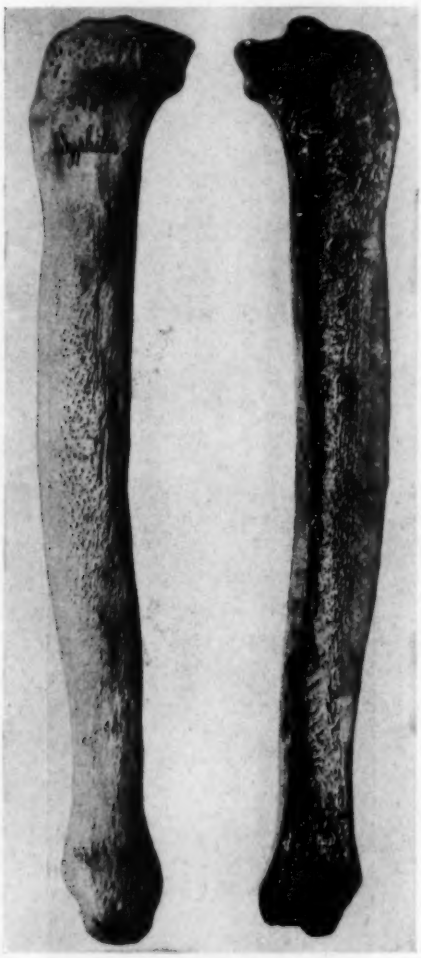

Fig. 4.—Syphilis of the tibia. The specimens are in the Pathological Institute, German University, Prague. The photograph was furnished by Prof. A. Ghon. Note the openings for blood vessels, many of them running longitudinally on the outer surface. On the right hand side of the section of the bone, the so-called "border stripe" is visible in the photograph, though not very distinct; this indicates a new growth from the periosteum.

such new bone may be dense like ivory; it is heavier than normal (figs. 4 and 5).

In general, investigators lay stress on the new formation of periosteal bone in syphilis (fig. 6). In dried bones, such periosteal growth may be demonstrated by means of the x-ray or in sections, gross or microscopic. The use of the x-ray for the diagnosis of syphilis of bone has been developed especially by Ludwig Pick and his pupils. According to Wilhelm, roentgenograms show marked formation of periosteal

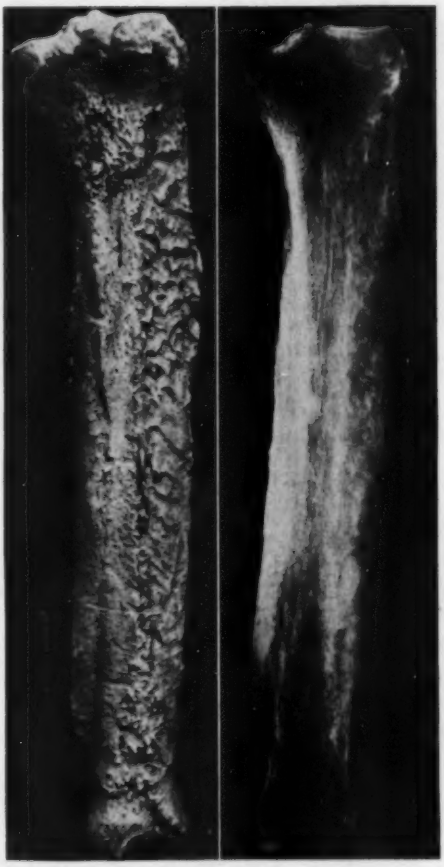

Fig. 5.—Syphilitic osteoperiostitis. The photograph and roentgenogram are published by the courtesy of Prof. Ludwig Pick, Berlin, and Dr. Seymour Wilhelm, New York. This is case 4 of Dr. Wilhelm.

bone, more or less narrowing of the marrow cavity and a sclerotic or finely porous quality of the new bone tissue; such fine meshes run in the long axis (fig 5). Articles by Weber, by Nestmann and by Michäelis have appeared recently, all having for their objective the diagnosis of syphilis in ancient bones by means of the microscope. Weber laid stress on the detection of a stripe (Grenzstreifen) marking

Fig. 6.—Syphilis of a long bone; × 10: *A*, active gumma; *B*, new formation of bone from the periosteum, a short distance from a gummatous lesion. Several long bones were involved. (Case from the Buffalo City Hospital.) (Original photograph.)

the boundary, where the new periosteal bone has been laid down on the old bone. He emphasized the value of detecting Sharpey's fibers in the new periosteal bone; in my experience, Sharpey's fibers are so difficult to see that they give aid only occasionally. In cases of long standing, the new periosteal bone may show haversian systems with concentric lamellae; the transition to the underlying bone may be gradual, and the boundary stripe not discernible. Michäelis thought that Wilhelm and Weber had overestimated the importance of periosteal growth of bone in syphilis; one may be unable to demonstrate it in cases of undoubted syphilis.

Fig. 7.—Periostitis and osteomyelitis with new growth of periosteal bone; × 10. The case (University of Buffalo case 6182) was one of compound fracture of the femur in a child, with resulting infection. No callus formed. The femur was amputated. A mantle of new, soft, periosteal bone extended along the shaft of the femur for 15 cm. from the seat of fracture. The marrow spaces were crowded with leukocytes. (Original photograph.)

DIFFERENTIATION OF SYPHILIS FROM OTHER PATHOLOGIC CONDITIONS

Acute osteomyelitis with periostitis may also lead to new growth of periosteal bone (fig. 7), though less frequently than does syphilis. It is more likely, than syphilis, to affect single bones and to lead to the formation of sinuses and sequestrums. The appearances of the bones vary enormously in different cases. In the absence of other data, in a single

dried bone it may be quite impossible to distinguish it from syphilis by any means of diagnosis known. Tuberculosis commonly causes destruction, but not regeneration, of bone. In a considerable number of rather rare chronic infections, such as leprosy and actinomycosis, the bones, it is said, may be affected, and some new growth may occur; on account of their rarity, these are not likely to lead to errors in diagnosis. Yaws (frambesia) is said to show tertiary lesions of bone similar to those found in syphilis and giving a roentgenogram like that of syphilis. Some roentgenograms from cases of tropical frambesia sent me by Professor Schüffner, of Amsterdam, show proliferation of bone different from any I have seen in syphilis or other conditions. The bone lesions of yaws seem not to have been thoroughly studied; from the information available I should think they were much less frequent and less extensive than those of syphilis.

In view of the tremendous new growth of bone often seen in the healing of fractures it cannot be doubted that new growth of bone takes place after injuries of the periosteum in which there has been no visible fracture and no infection.

The rather rare hypertrophic pulmonary osteo-arthropathy of Pierre-Marie (Crump) may lead to general formation of osteophytic growths that might be mistaken for those seen in syphilis. Sjövall and Michäelis believed that this mistake in diagnosis was made in the case of the skeleton of Magnus Ladulös, referred to farther on in this article.

In rickets there is sometimes new growth of periosteal bone; however, rickets has rarely been found in bones from ancient times. Symmetrical osteoporosis of the cranium may show osteophytic growths; it was common in ancient America, but should be recognized by its gross appearance (Williams, 1929).

The condition, or conditions, called osteitis deformans, Paget's disease, osteitis fibrosa (of von Recklinghausen) or osteodystrophia fibrosa may produce changes in the bones indistinguishable to the naked eye from the diffuse, nongummatous form of syphilitic osteoperiostitis. This subject was discussed at great length at a meeting of the German Pathological Society in 1926 (Christeller). At that time the tendency among many German pathologists seems to have been to consider the osteitis fibrosa of von Recklinghausen and the osteitis deformans of Paget as different phases or different stages of one and the same process. That is the attitude of Kaufmann, in the American edition of his "Lehrbuch der pathologischen Anatomie," translated by Reimann, 1929. In some more recent articles, and since this portion of the present paper was first written, certain observers, who formerly regarded osteitis fibrosa and osteitis deformans as aspects of a single process under the

name of osteodystrophia fibrosa, now consider them entirely different processes. Among English pathologists, Turnbull, in a publication of October, 1931, discussed their points of resemblance and difference without stating a definite opinion. Lang regards osteitis fibrosa as a secondary result of some preexisting disease of the bones; he believes osteomalacia and rickets are the most important underlying factors in

Fig. 8.—Osteodystrophia fibrosa—Paget's disease—a saber-shaped tibia of a man, aged 77, with arteriosclerosis. The photograph and the roentgenogram are published by the courtesy of Prof. Ludwig Pick, Berlin.

cases of widespread osteitis fibrosa. Knowledge of the relations of the diseases in this group to one another is passing through a transitional period at present. One is sometimes uncertain as to an author's meaning when he writes of osteitis fibrosa or osteitis deformans. Furthermore, some cases are difficult to classify on morphologic evidence alone (see figs. 9 and 10).

Fig. 9.—Osteodystrophia fibrosa, active, still progressing (case 6131, University of Buffalo). The roentgenogram permits one to see the phalanx in the center without much reduction in size. The roentgenogram was furnished by the Marine Hospital, Buffalo, N. Y. The classification of this case is somewhat in doubt; some features of it even suggest osteomalacia: It occurred in a man, aged 56. There were two fractures of the right femur and one of the right tibia; the left femur was bent outward in its upper part. Roentgenograms showed slight thickening and some mottling of the vault of the cranium. Several of the bones of the arms showed lamination, and one humerus and ulna presented definite thickening from periosteal bone. The pelvis was mottled with light and dark areas. The right femur and tibia showed lamination. When the patient was last seen the x-ray pictures had revealed no tumors and no cysts; no examination for parathyroid tumors had been made. The involvement of the bones of the hand is said to be unusual. Figure 10 is a photomicrograph from the right femur of this patient.

Schmorl's recent article is based on the study of fifteen cases of generalized osteitis fibrosa and one hundred and ten cases of osteitis deformans. It seems to me that these diseases must be commoner in Europe than in the United States. I have seen only a few cases of them. Schmorl found cysts of bone, "brown tumors" (presumably giant cell tumors) in the bones, and the (so-called) tumors of the parathyroid bodies in his cases of osteitis fibrosa; he did not find them in his cases of osteitis deformans of Paget. Although a final verdict on the pathogenesis of these diseases must be deferred, it seems that, while the microscopic structures of the two are very similar in the early

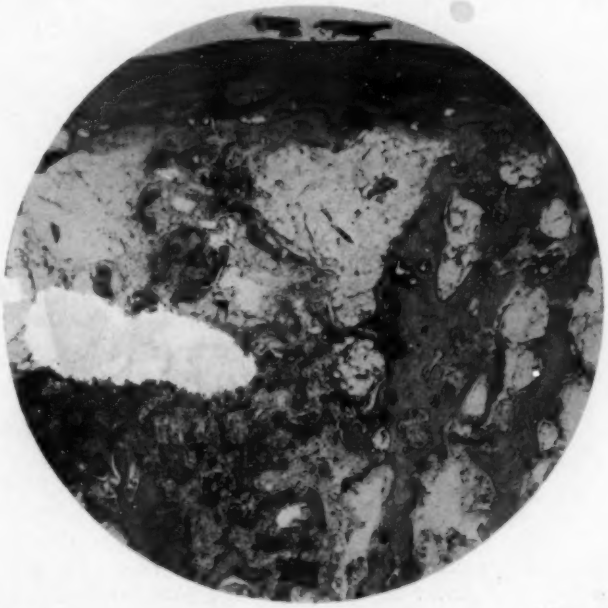

Fig. 10.—Osteodystrophia fibrosa (case 6131, University of Buffalo); right femur; section stained with hematoxylin and eosin; × 14. The section shows the fibrous and cellular marrow, with some fatty marrow, and a small amount of irregularly disposed new formed bone. High power magnification shows many osteoclasts and osteoblasts, and poorly developed mosaic structures in the new bone. See figure 9 for a roentgenogram from the same case. (Original photograph.)

stages, the amount of new soft bone formed is greater in Paget's osteitis deformans. This is, therefore, the form more likely to be confused with syphilis in making a diagnosis on dried bones. Denninger recently described osteitis fibrosa in the skeleton of a prehistoric American Indian; Pales reported cases of osteitis deformans and osteitis fibrosa in neolithic bones from France.

Paget's osteitis deformans is likely to involve a large number of bones in the same person, although single bones may be affected. The bones are enlarged, their surface may be irregular, they may bend, there may be a saber-shaped tibia, the marrow cavity is usually large or is filled with spongy bone. Fractures of bones may occur, but they are less frequent than in osteitis fibrosa, according to some observers. The fully formed new bone is said to look, on section, like pumice stone. The bones sometimes present cavities like cysts (Turnbull); cysts are said to be rare. The skull may be very thick. Some investigators regard certain cases of leontiasis ossea as belonging in this cate-

Fig. 11.—Mosaic structures from a section of the skull in a case of Paget's disease (not the case shown in figure 8). The photograph was furnished by Prof. Ludwig Pick.

gory. It can usually be shown that the changes in Paget's disease do not lead to new formation of bone by the periosteum as is so commonly the case in syphilis (see Freund and Schmorl in a later paragraph).

According to Ludwig Pick and his pupils (Wilhelm), the roentgenogram gives a characteristic picture in Paget's osteitis deformans: The marrow cavity is large, the new formed bone appears split into lamellae running lengthwise with the bone, and most characteristic of all is the absence of any new growth of bone from the periosteum (figs. 8 and 9). However, "compensatory" periosteal growth apparently may occur in rare cases of Paget's osteitis deformans (Weber). I have a roentgenogram that I interpret as being from such a case. Freund attributed the thickening of the shaft of long bones to "parosteal" growth in the

adjacent fat and connective tissue. Schmorl (1930) found new periosteal growths of bone as much as from 5 to 6 mm. in thickness; the mosaic structures described in a subsequent paragraph were lacking in them. Pick thought that such growths, occurring coincidently with growth in the cortex of the bone, would not appear in roentgenograms as being separated from the cortical growth.

Most observers agree that the changes in Paget's osteitis deformans are not inflammatory. Recent studies suggest that tumors or hyperplasias of the parathyroid bodies or excessive secretion from these bodies of a hormone influencing calcium metabolism may be the cause in some cases of osteitis fibrosa (Hunter and Turnbull; Jaffe, Bodansky and Blair). There is evidence suggesting that some cases called osteodystrophia fibrosa or osteitis fibrosa (Christeller, Grauer) result from improper food; that may have been important among ancient and primitive people.

Whatever the cause may be, the process consists of a resorption of bone with rebuilding of irregularly disposed bone (fig. 10). The formation of new irregularly disposed lamellar bone produces in its final stages what Schmorl called "mosaic structures." Sections of the new bone, under moderately high power, show that it is traversed by numerous short, irregularly running lines of cement substance, giving the impression that the tissue is made of many small pieces put together like a mosaic (fig. 11). Schmorl regarded the mosaic structures as pathognomonic of osteitis fibrosa in his paper of 1926. More recently (1930), he separates osteitis deformans from osteitis fibrosa, where he formerly regarded them as aspects of one process. He now finds the mosaic structures extensively and typically developed in osteitis deformans, while they are fewer and more regular in their course in osteitis fibrosa. An illustration in Paget's original article seems to me to show the mosaic structures. Freund remarked that the cement lines are broad, and that they stain deeply. The mosaic structures are well illustrated in Schmorl's article of 1930.

As the mosaic structures could be demonstrated in dried specimens, Schmorl suggested using them to differentiate between osteitis fibrosa (I understand that he would now say osteitis deformans) and syphilis in ancient bones. Nestmann found that the mosaic structures were present over limited areas in one case of syphilis of bone, his observation being verified by Schmorl. Michäelis was apparently not aware of Nestmann's observation when he said: "The mosaic structures separate osteodystrophia fibrosa from all forms of bone syphilis." Pick has seen mosaic structures in recent syphilitic hyperostoses. Schmorl said that they appeared in other bone diseases also, but that these were not comparable to the mosaic structures of osteitis deformans.

TECHNICAL POINTS IN EXAMINATION OF ANCIENT DRIED BONES

In my experience, careful examination with the naked eye, including inspection of the bone after it has been sawed lengthwise, furnishes more information than can be obtained by any other single method. By these means one can usually determine whether or not a new growth of bone is periosteal in origin. The dried bones should be moistened slightly; they can be sawed better when they have been soaked for several hours in about 5 per cent formaldehyde solution. Weber insisted that in preparing sections for examination with the microscope, pieces be taken from several parts of the bone at some distance from one another. Even in old bones preliminary fixation in formaldehyde is desirable. Decalcification in 1 to 5 per cent nitric acid and embedding in celloidin may be carried on as described in any book on histologic technic. With fragile material, decalcification with nitric acid may be accomplished after embedding in celloidin. I have found that, except for the cells, the minute structure may be preserved perfectly in very ancient bones from countries having a dry climate, such as Egypt and Peru. More recent bones, presumably buried in a moist soil, as from the southern part of the United States, have lost a large part of their organic matter, and sometimes are infiltrated with mineral salts, presumably calcium; sections can only be made by grinding. The use of the expression "fossil bone" to indicate that a specimen is ancient, as is often done by anthropologists, is misleading; recent bones may be fossilized and old ones not. Microscopic fields having the original framework well preserved may lie haphazard among fields where the structure is blurred or lost.

Weber experimented with ground sections of bone, both thin, for transmitted light, and thick, which he examined by reflected and polarized light; the use of thick sections he considered applicable to ancient bones in which the organic matter had been replaced by calcium and other salts (so-called fossil bones). His technic was admirable and was worked out with immense detail, for which his article must be consulted. He found that with thick sections examined by reflected light he could demonstrate enough of the finer structure of bone to be of assistance in differentiating syphilis from other diseases of bone, such as Paget's osteitis deformans. Michäelis applied the technic of Weber to recent normal and diseased bones; also to some ancient bones in the case of which the diagnosis was in doubt. His results will be considered on the succeeding pages. Both Weber and Michäelis gave good photomicrographs of their sections. In some of their plates new growth of periosteal bone is evident, but I must admit that I am unable to see some of the finer histologic changes that they describe.

SUMMARY

The skull is most important: Extensive involvement of its upper surface, the so-called "caries sicca," new formation of bone, irregular and stellate scars and the "worm eaten" appearance justify the diagnosis of syphilis in all reasonable probability. Involvement of the nasal region, with new growth of bone is frequent, but caution must be used in these cases, as there are several other infections that may affect the nasal region, usually without much formation of bone, however.

In syphilis, in nonsyphilitic periostitis and in Paget's osteitis deformans, the shafts of the long bones may show irregular thickenings. It is usually impossible to differentiate between these conditions by examination of the exterior of a given long bone. The bone should

be roentgenographed, sawed lengthwise and sections made for examination with the microscope. In some cases, the diagnosis must remain in doubt.

In syphilis, the new-formed bone is largely periosteal in origin and often dense; encroachment on the medullary canal is characteristic. Sinuses and sequestrums are uncommon. Involvement of two or more bones of the extremities is in favor of this diagnosis.

In nonsyphilitic periostitis, the new-formed bone is usually periosteal. It is unlikely to encroach on the medullary canal. In periostitis connected with infectious osteomyelitis, the bones are likely to have sinuses and sequestrums. Usually single bones are involved.

In Paget's osteitis deformans, the new-formed bone is rarely periosteal, but future studies may show that periosteal bone is formed more often than has been believed. The new bone is usually not dense, but porous. The medullary canal is likely to be large. Usually several bones are involved. The mosaic structures described by Schmorl may eventually be of assistance in making the diagnosis; I have not found the results described to date convincing.

The recognition of Spirochaeta pallida in doubtful ancient bones, a suggestion that has come to me from some anthropologists, hardly merits serious consideration. It is just possible that spirochetes could be detected in the dried soft parts of mummified bodies. The recognition of syphilitic aortitis in a mummy is well within the range of possibilities. I have been able to secure a good specific stain in the elastic tissue of the aorta of an Egyptian mummy of the Eighteenth Dynasty (about 1000 B.C.).

REVIEW OF ALL REPORTED CASES OF ANCIENT SYPHILIS OF BONE

It is probable that I have overlooked some reports, as many of those that I have found were published in journals of archeology and ethnology, or in the transactions of similar societies and museums. Such publications are often difficult of access, and apparently no general index exists for all of them. I hope that nothing important has been overlooked. Considerable confusion has been created when a case or a specimen has been described by different authors under different names. Although many specimens have been described as showing ancient syphilis, in only a few of the cases are the presentations plausible enough to make them important. Those that seem to me not important I am considering as briefly as possible, but I am including them for the sake of completeness. The important cases are described in greater detail and are discussed in the summary at the end of this paper. For the sake of convenience the cases will be taken up by countries beginning with Japan.

JAPAN

Adachi described certain long bones from shell heaps in Japan, stated to be of the stone age, i. e., more than twenty-five hundred years old, that show changes which were pronounced by Yamagiwa to be those of syphilis. The same specimens were described by Dohi, with illustrations; Dohi did not feel certain that they are syphilitic, and was also uncertain as to their antiquity.

These bones are a tibia and a fibula, both showing thickening and roughening of the shaft; the two are united by a kind of bridge of bone about their middle. The outer surface of the tibia presents a depression that might have been produced by ulceration. Dohi noted that the stellate scars described by Virchow as characteristic of syphilis are not present. I have not been able to secure original photographs of these bones. The illustrations published by Dohi are not clear enough to warrant reproduction. His illustration showing the bridge of bone referred to seems to me to suggest injury as a cause for the changes seen, or possibly a healed osteomyelitis with periostitis. I do not know of any roentgen or microscopic studies made of these bones.

EGYPT

Certain bones from Egypt, said to be more than twenty-eight centuries old, were described in 1900 by Dr. Zambaco, pasha, as syphilitic. I am indebted to the article of Raymond (1911) for the facts. It was stated that Fournier did not agree with Zambaco, and that the matter was referred to a committee of the Academy of Medicine of Paris, but the committee never rendered a report. Raymond seems to have rejected these specimens. They were also referred to by Bloch, who quoted the criticisms of Bayet and Fournier.

The Roda Skull.—This skull has been described by Lortet and by Lortet and Gaillard. It is now in the Museum of Natural Sciences, Lyons, France, where I had the opportunity of examining it carefully in August, 1925 (fig. 12).

The skull is stated to have come from a prehistoric cemetery at Roda, Upper Egypt. It is a small skull, probably belonging to a young woman. The lower jaw is missing; the last molars in the upper jaws are not erupted; the teeth have fallen out post mortem, except three bicuspids, which are in good condition. Part of the left temporal bone has been broken off post mortem. The palate and facial bones are normal. The skull is remarkably well preserved for one of such antiquity; it has a beautiful yellow-brown patina, like old ivory. The supposed syphilitic lesion consists in erosion starting from the outer table of the cranium. This erosion is less marked on the frontal, the right parietal and the occipital bone. It is most marked on the left parietal bone at its upper, anterior portion, where an irregularly shaped portion of the outer table has been removed, and at two points there are small perforations completely through the inner table. At several places, the patination is darker on the outer surface and becomes lighter according to the depth of the excavation. This, I should suppose, is what would have happened if the erosion had occurred after time had given the skull its brown color. There is no new formation of bone. In my opinion, this is not a syphilitic skull, and the erosion that it presents was the work of some rodent animal. Elliot Smith (1908) wrote of a

beetle that erodes bones in Egypt, and ascribed the changes in the Roda skull to this beetle, as well as the changes early described by Fouquet in bones from Egypt, regarded by Fouquet as evidences of syphilis. Gangolphe and Raymond also expressed the opinion that the Roda skull was not syphilitic. Apparently this is the skull referred to by Moodie in his "Paleopathology," p. 411; the drawing that he gives does not look as though it could have been made from the same skull (Moodie's plate LXXXVI). I have introduced a photograph of this skull, as it affords an example of the kind of case that has led to confusion through incorrect diagnosis.

Nubian Bones Described by Michäelis.—Michäelis described briefly certain bones furnished by Sir Arthur Keith from the Hunter Collection of the Royal College of Surgeons, London. These bones, dated

Fig. 12.—The Roda (Egypt) predynastic skull, the lesions in which, in my opinion, have been incorrectly diagnosed as syphilitic. According to Prof. G. Elliot Smith, the erosions were probably produced post mortem by beetles. The photograph was furnished by Prof. M. C. Gaillard of the Museum of Natural Sciences, Lyons, France, where the specimen now is.

around 1000 B.C., are said to be of Nubian origin; no other facts as to their origin are given. Of these specimens, a femur and a tibia are pronounced by Michäelis as probably syphilitic. From his illustrations of the gross appearance of these bones I should think his suspicion justified, although the pictures are too small and too indistinct to permit more than a guess, and other causes of periostitis would be equally probable. I can make nothing of his photomicrographs of the finer structure of the bones (Michäelis, pp. 54-65 and pp. 85-87, especially p. 87, and plate XXXVI).

Negative Evidence from Egypt.—There is a large body of negative evidence as to ancient syphilis in Egypt. It is important because of the great antiquity of civilization in Egypt, with its attendant factors, the formation of large settled communities and the having commerce and intercourse with foreign peoples. Investigators of recent years, Elliot Smith, Wood-Jones, Derry, Dawson, Ruffer and Oetteking, are unanimous in stating that they have found not a single specimen of ancient bone from Egypt showing changes that could be called the result of syphilis. The fact that they usually made such statements is proof that they were on the lookout for this disease. Elliot Smith informed me that he had found not a single syphilitic skull in more than 25,000 ancient Egyptian skulls examined by him.

Ruffer and Rietti referred to unfinished excavations at Alexandria, Egypt, that would, when completed, include the crypts containing the skeletons of the prostitutes who accompanied the Greek army of Alexander the Great. The inscriptions on the tombs were said to give this information. They remarked, "Here, if anywhere, evidences of syphilis and gonorrhea should be found, provided venereal disease existed at that period." The excavations were in charge of Dr. Evaristo Breccia, curator of the Musée Greco-Romain at Alexandria. Dr. Breccia informed me that but two of these tombs were in question; these tombs have since been opened, but they had been invaded by mud and water, so that no useful information could be derived from their contents.

FRANCE

A considerable number of ancient bones from France alleged to show the lesions of syphilis have been described. Raymond discussed many of these cases, and I am indebted to his articles for a large part of the statements given in what follows, though I cannot agree with his conclusions. Some of these bones appear to have been mentioned first in a thesis by LeBaron (1881), which is not accessible to me; his most important specimen is said to have been lost. A certain amount of confusion has been created by the views of Parrot on a relation between congenital syphilis and rickets, views that have long since been discredited, but that some writers have taken seriously in recent years. Confusion has also resulted when various authors have discussed some of the same cases in different orders and under different designations (Buret, LeDouble, Gangolphe). Bloch referred to most of those described up to the time his book was written, 1911. A nearly complete list of them was recently made by Pales, who took a conservative position. Valuable testimony was given by Jeanselme, who said that the anthropologic collections of Europe contain no document not subject to criticism, and no bone or tooth that is a proof of the antiquity of syph-

ilis; he had made extensive researches in the museums of Paris, without result.[6]

I shall take up what seem to me the most important specimens first.

The Tibia from Solutré, France.—As far as I know, this specimen has not been the subject of any special article, although it is mentioned by several writers. In one of his two papers on the Roda (Egypt) skull, Lortet said that syphilis had been demonstrated in a female skeleton from Solutré, which had been carefully examined by Broca, Virchow, Parrot and Rollet, and that these investigators agreed that the changes shown on the tibias were certainly syphilitic.[7]

In August, 1925, I examined this specimen, which is in the Museum of Natural Sciences in Lyons, to which it was presented by the finder, M. l'Abbé Ducrost (fig. 13). According to my notes, the right tibia had three enlargements anteriorly, one near the middle, one a little above it and another a little below it. The two lower were spindle-shaped and involved the anterior crest; the upper one was on the inner side. Each was about 4 or 5 cm. in length. The surfaces were smooth, except for being rendered a little porous by openings for the transmission of blood vessels. The bone was intact and had not been sawed at that time.

In my opinion, it is possible that these hyperostoses were caused by syphilis, but there is nothing characteristic about them, and there were several other possible causes besides syphilis, such as injury. The information that I was able to obtain indicated that the skeleton was regarded as prehistoric, but that no definite date could be assigned for it. In this connection, it may be pointed out that the dating of skeletal material from Solutré is beset with many uncertainties. The opinion credited by Lortet to Virchow is inconsistent with Virchow's own published utterances. Gangolphe and Raymond appeared to regard the Solutré tibia as giving evidence of syphilis, but agreed that its age is uncertain, though the specimen is ancient. Raymond stated that it may not antedate the barbarian invasion, and that it most probably corresponds with the Roman period. Several writers referred to this specimen without giving any new information. Pales recently reviewed the case and gave the most complete account of it that I have seen. He reproduced a roentgenogram of the bones that seems to indicate that the hyperostoses consist of rather dense bone. He also mentioned a small hyperostosis on the left tibia of the same skeleton. He seemed to think a positive diagnosis could not be made.

The Long Bones of de Baye from the Valley of the Marne.—These specimens have given rise to more discussion and controversy than any other find that I know of.

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6. "Les galeries anthropologiques d'Europe ne contiennent pas un seul document qui ne prête à la critique, pas un seul os, pas un seul dent, qui puisse être consideré comme une preuve de l'antiquité de la syphilis. Les longues et patientes recherches que j'ai poursuivies ici-même au Musée de l'Ecole et de la Société de l'Anthropologie ont eté sans resultat."

7. ". . . on en (syphilis) a constaté la présence dans la station de Solutré, sur un squelette de femme, actuellement au Muséum de Lyon, et jadis examiné avec beaucoup de soins par Broca, Virchow, Parrot et Rollet, qui ont eté unamines à conclure que les alterations que présentent les tibias de ce squelette sont certainement de nature syphilitique."

Certain burial caves artificially cut in the chalk of the valley of Petit-Morin in the region of the Marne, France, were explored by Baron J. de Baye. The results were reported at various times between 1874 and 1888. The collections made by de Baye were given to the museum at Saint-Germain. A study of the bones of this collection was undertaken by Raymond (1911, 1912), who found among them a humerus and an ulna that he believed showed evidences of syphilis.

Fig. 13.—Ancient tibia from Solutré, France. The nodes may have been produced by syphilis or may be due to some other cause. The photograph was furnished by Prof. M. C. Gaillard of the Museum of Natural Sciences, Lyons, France, where the specimen now is.

My information has been obtained from Raymond's article chiefly. Raymond stated that there could be no doubt as to the period to which the bones belong, that it was the latter part of the neolithic; a few bronze ornaments were discovered, indicating that the neolithic period was approaching its end.

The humerus and ulna in question were not known to have belonged to the same individual (fig. 14). They were carefully described as to

their gross appearance by Gangolphe. The humerus was heavy; it presented a hyperostosis over an extent of from 16 to 17 cm. of its lower and middle thirds, with small openings for the passage of blood vessels; the medullary canal was large; the thickening seemed to be due to the formation of layers of periosteal bone. The process was, how-

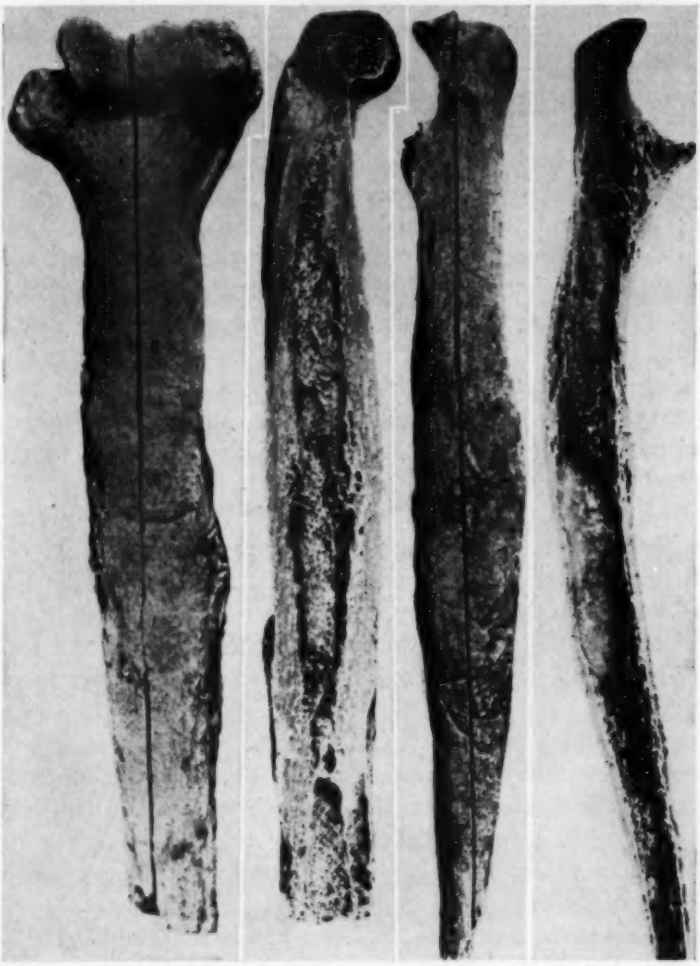

Fig. 14.—A humerus and an ulna found by de Baye in a burial cave in the valley of the Marne, France. They are said to be neolithic, and are regarded by some as showing the effect of syphilis. The illustration is copied by permission of Dr. Paul Raymond, Paris. Compare with figure 8.

ever, pronounced to be central and to have been a tertiary, gummatous, infectious osteomyelitis. The ulna was light; it was enlarged in the upper part of the diaphysis for from 13 to 15 cm., the surface showing

minute orifices. The new periosteal layers were traversed by fine canals, as were the remains of the old shaft; the medullary cavity was much enlarged, and in it was a cavity with definite walls. The ulna was regarded as having diffuse, gummatous osteomyelitis. The absence of sequestrums and of evidence of suppuration in both bones was considered an important argument in favor of syphilis.

Raymond and Gangolphe stated that the specimens were examined by Lannelongue, and that they were pronounced syphilitic by him. Gangolphe also said that Lannelongue believed that the hypertrophying osteitis of Paget was a manifestation of syphilis, a view that Gangolphe himself formerly held, but that he no longer entertained.

A brief account of these specimens was given by Pales, with photographs; he offered no personal opinion, but stated that Professor Jeanselme did not appear to agree as to their specific (syphilitic) nature. They were also briefly described by Vorberg, with photographs; his description apparently called the attention of some German observers to them.

Having been quoted by Vorberg as pronouncing the specimens of de Baye syphilitic, Aschoff published a brief note stating his position. He had not seen these bones, but admitted the great similarity of the photographs of them to recent bones known to be syphilitic, of examples of which he gave excellent photographs. He could not give final judgment without personally examining the bones in question. Even then, he said, though there might be the greatest similarity in the findings, that did not prove their identity.

Christeller thought from Vorberg's illustrations that the condition in the de Baye specimens resembled osteodystrophia fibrosa more than it did syphilis.

Weber, working in Aschoff's laboratory, examined various known and doubtful cases of bone disease, as stated in the preceding section of this paper. He concluded that the bones from the Marne (de Baye) were like syphilitic bones, but that they might be from a case of osteodystrophia fibrosa. Study of these bones with the microscope was much to be desired.

The bones of de Baye were studied again in 1930 by Michäelis, who obtained portions of them for examination with the microscope. He concluded that nonspecific osteomyelitis, osteodystrophia fibrosa and the osteo-arthropathy of Pierre-Marie could be excluded. He did not find the mosaic structures of Schmorl, and stated that the participation of the periosteum in the new formation of bone could be seen. (The last is not clearly shown in his photomicrographs.) Michäelis made a diagnosis of syphilis, with such degree of probability as present knowledge permits.

As I have not seen these bones, I am in no position to speak of them with authority. However, I am surprised that so little has been said, by the various observers who have written of them, concerning the large cavity in the middle of the shaft of the ulna, plainly discernible in the photograph of the ulna after it had been sawed, a point in favor of osteodystrophia fibrosa. As far as I can learn from the literature, no roentgenogram of the specimens has been published. Evidently, in the present state of knowledge, no final verdict can be given in this case.

Michäelis described several " bones of the 'stone age' " obtained from the Museum of Saint-Germain-en-Laye, near Paris (fig. 15). Of these, an ulna (his Präparat 30[8]) and a femur (his 31) showed changes that he diagnosed as probable syphilis on the strength of the gross appearance and apparent evidence of periostitis in the section (poorly shown). The condition presented by another femur from the same source (his 34), a fragment, he diagnosed as syphilis by exclusion. His illustrations certainly show new growth of bone from the periosteum. Apparently Schmorl concurred in this opinion. It may be pointed out here that exclusion of osteomyelitis and nonsyphilitic periostitis from such a fragment, in which both ends of the bone were missing, cannot possibly be done to a certainty, or even with probability.

Other Material, Mainly from France.—The descriptions of the remaining cases from France are in no way convincing, but the cases are mentioned briefly for the sake of completeness.

The skull of Braye-sur-Seine is to be regarded as an example of the lesion that followed the cauterization practiced in prehistoric times, and fully described by Manouvrier. It was first brought forward as presenting syphilis by Parrot.

Bones and teeth from the dolmens of the Lozère (Cauquenos or Boujassac) excavated by Prunières are not to be regarded as showing ancient syphilis, according to Raymond. They were also presented by Parrot.

A tibia from the dolmen of Maintenon (Eure-et-Loire) was described by LeBaron as having multiple exostoses: The specimen was in the Musée Broca, but appears to have been lost (Raymond, 1911).

A fragment of frontal bone from a tumulus of Méloisy (Côte-d'Or) was described by LeBaron as having two exostoses at the left of the coronal suture, diagnosis uncertain; the specimen cannot now be found. Raymond discovered another skull from the same tumulus with a loss of substance on the frontal bone that he thinks might be due to syphilis.

A tibia from the dolmen of Léry (Eure) was described by LeBaron as his best proof of the existence of ancient syphilis; Raymond appeared to agree with him. The only description given by him is that hyperostosis was present. According to Pales, the specimen seems to have been lost.

The occurrence of these bones in dolmens or tumuli indicates that they probably belonged to the neolithic or to the bronze age; possibly to a later period.

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8. On Michäelis' plate XLVI, the ulna seems to have been incorrectly numbered 28, no doubt through an error of the printer. The arrangement of the illustrations and of the text in this monograph is such that I followed them with difficulty and some uncertainty.

Pales also mentioned among the bones that others had called syphilitic a neolithic femur on which he made the diagnosis of Paget's disease (his plates IV-VI), a parietal bone having osteoporosis (his plate XLIII, fig. 2), and various other bones having lesions that he regarded as not syphilitic. He gave illustrations of a neolithic humerus on which he made the diagnosis of osteitis fibrosa (his

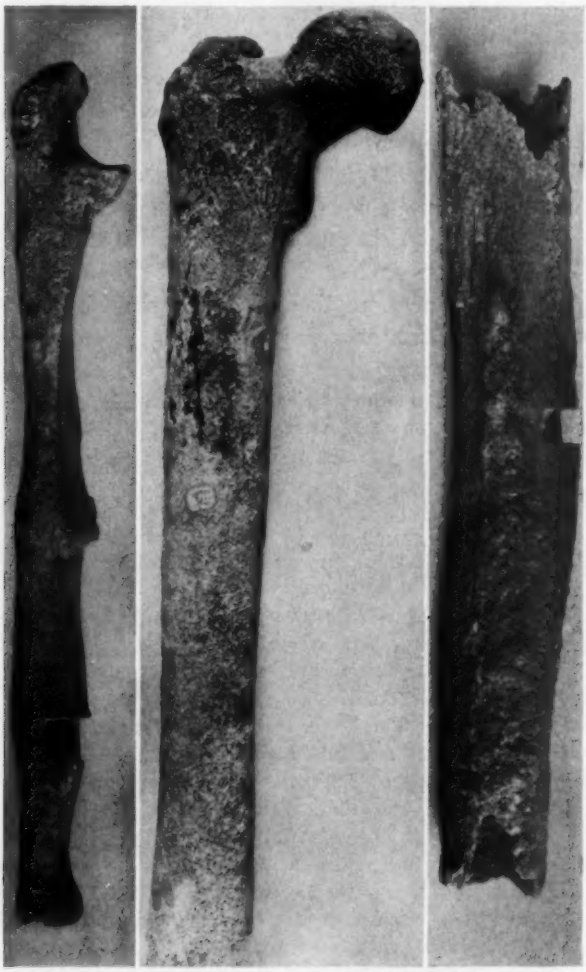

Fig. 15.—"Stone Age" bones. The photograph was furnished by the Museum of St. Germain-en-Laye, France. These bones were discussed by Michäelis; his numbers (from left to right) and diagnosis were: 30, ulna, suggestive of syphilis; 31, femur, suggestive of syphilis; 34, femur (fragment), syphilis.

plates X and XI, roentgenogram), and a neolithic femur and tibia called examples of osteoperiostitis (his plate XXXV), that some might suspect of being due to syphilis.

Saint-Perier described what he believed to be an example of congenital syphilis, of uncertain date but probably of the Gallo-Roman period, found at Souzy-la-

Briche, near Etampes, France. The specimen was the somewhat fragmentary skull of a child, thought to be about 8 years of age. The teeth were not "Hutchinson teeth," but some had fallen out. The pathologic condition consisted of elevated areas on the frontal bones that presented "une apparence criblée"; the same appearance was visible to some extent on the upper surfaces of the orbits and on the right parietal bone. The rest of the skull and such long bones as were found were free from this appearance. From the description and the excellent drawing that accompanies this article, I should be of the opinion that the case was one of symmetrical osteoporosis of the upper surface of the cranium (cribra parietalia), and certainly not one of syphilis; however, I have not seen the specimen.

Raymond said further (1911) that no gap exists between prehistoric times and the end of the fifteenth century, because there are some convincing cases of syphilis of bone from the old world of this period. He does not, however, give any details concerning the evidence on which his statement is based.

In another article (1912), Raymond spoke of certain bones presented before the Société de dermatologie in 1894 from a hospital of the Templars found associated with a coin of Verona of the twelfth century. He gave no additional facts.

Spillman described a skull attributed to the Merovingian period, that showed a small depressed scar and had a "worm eaten" appearance; this might have been a healed gummatous lesion or might have been due to traumatism or to cauterization, as he suggested. He gave no illustrations and did not tell where this skull was. He referred to exostoses on the tibias from certain Gallic burials at Nod-sur-Seine, described by Brulard (*Revue préhistorique de l'est de France,* which is not accessible to me).

A case that is supposed to have originated in France, but in which death occurred in Geneva, Switzerland, is mentioned in a brief communication by H. Maillart. In a history of the cathedral of St. Peter, an account is given of the examination in 1869 of the body of a bishop, who came to Geneva from Paris in 1422, dying in 1423. The description of the bones was written by the professor of pathologic anatomy, Zahn. The femur and tibia were stated to show extensive thickening from a combination of osteoporosis and osteosclerosis. The results were pronounced characteristic of syphilis; no illustrations were given. The condition of the cranium was not stated.

Bloch mentioned several specimens in which the lesions were alleged to be those of ancient syphilis: one skull from England, said to be of the time of Richard III, referred to by Carter Blake; a skull from the dolmen of L'Aumede, demonstrated by Broca; various bones from a cemetery on the Rue de Bruxelles in Paris (but of uncertain date), also mentioned by Broca, and (p. 346) a skull of the Merovingian period produced by de Mortillet, and having certain horizontal grooves on the teeth. None of these seems to be of importance, but they are mentioned for the sake of completeness, and because I have not seen references to them in the other authors cited.

In the case of the ancient Swedish King, Magnus Ladulös, reported by Fürst and Olsson (apparently as a case of syphilis), in whom several long bones were involved, Michäelis obtained a portion of the tibia for examination. As this tibia in sections showed undoubted periostitis without severe alterations of the compacta, and as several bones were involved, the condition could not be local periostitis. He regarded it as most probably Pierre-Marie's hypertrophic osteo-arthropathy (Michäelis, pp. 86 and 88; also plates XL-XLIII, all photomicro-

graphs). Professor Sjövall had already published an opinion to the effect that this was probably Pierre-Marie's osteo-arthropathy.

The original articles in Swedish are not accessible to me, and my information is obtained wholly from the monograph of Michäelis.

SYPHILITIC BONES, DATED SOMEWHAT DOUBTFULLY AS ABOUT FROM 1500 to 1600 A. D.

It may be impossible to assign exact dates to bones from cemeteries even of historic times. However, some specimens from a time probably near the year 1500 or later show evidence of syphilis, as far as it is possible to make a diagnosis from dried bones.

In his treatise on pathologic anatomy, Lancereaux described and gave drawings of a skull and a femur that appear to be syphilitic. He discussed the possibility that the lesions might have been produced by leprosy, and deplored the lack of information on the condition of the

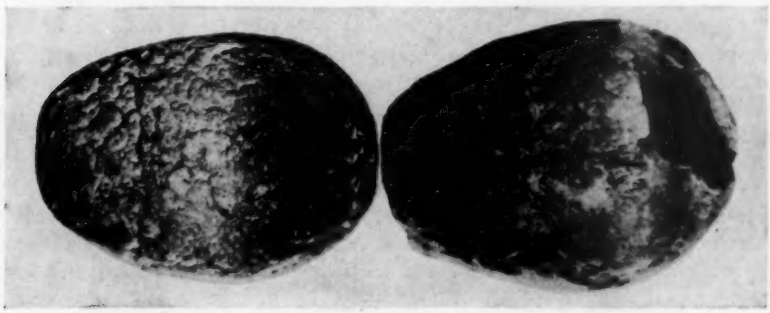

Fig. 16.—Syphilitic skulls, Paris, Lancereaux, probably of about the year 1500. (Original photograph.)

bones in leprosy. He stated that the specimens were obtained from the catacombs of Paris, but that they came originally from a cemetery on the Rue de Douai, on the site of an ancient leprosarium. Apparently at that date (1889), these catacombs were a promising field for further exploration, likely to yield many specimens showing bone diseases of past centuries.

On a visit to the Musée Dupuytren in 1925, where Professor Roussy gave me access to the splendid material collected there, I found two skulls, which, my notes state, were attributed to Lancereaux, and which came from an old leper cemetery of the fifteenth century. My copy of the label reads "733 and 734, Nouv. Lancereaux, Cimetière dit a Lepreux rue de Douai." My impression of the specimens was that they were as surely syphilitic as it is possible for skulls to be. I obtained fairly good pictures of them with a pocket camera, from which enlargements have been made (fig. 16). Apparently, the character of the

lesions was the same as that shown in Lancereaux's drawing. Whether or not one of them was the subject of his drawing cannot be determined.

Even if it is assumed that the cemetery on the Rue de Douai was used exactly until the year 1500 and no later, the changes in these skulls may have been some of the results of that devastating outbreak of syphilis that occurred at and after the siege of Naples. But the possi-

Fig. 17.—Syphilitic skull, Nuremberg, probably of about the year 1500. The photograph was furnished by Prof. Gustav Hauser, Erlangen.

bility that the lesions were caused by leprosy, as suggested by Lancereaux, might be kept in mind.

The bones found in an ossuary connected with the cathedral of the town of Cham in Bavaria were described by Jäger. Thirty-three skulls showing pathologic conditions had been preserved from some five thousand taken from the ossuary.

Jäger believed that two of them showed the changes of osteitis tuberosa syphilitica. The diagnosis was confirmed by von Hansemann, von Luschan and,

for the first specimen, by Kaiserling also. I have not seen these skulls, and it would be unsafe to form an opinion from the illustrations, but the descriptions seem consistent with the diagnosis given. The ossuary of Chammünster was in use during a long period through the Middle Ages, and in a few cases into the nineteenth centry. From the evidence available, Jäger believed that the two skulls belonged to about the year 1600. He also described a considerable number of long bones from the same source, on which he made the diagnosis of syphilis (confirmed by von Hansemann), and a skull and a lower jaw from an ossuary at Greding, the descriptions of which are less convincing and which were also less ancient.

Hauser described and discussed an old skull from the cemetery of the Sebaldus church in Nuremberg. The chronicles of the city stated that no burials had taken place after 1519. Hauser thought that the earliest possible record of syphilis in Nuremberg was for the year 1495, and that the date was more probably late in 1496. From these dates Hauser argued that the skull in question belonged to some time between 1497 and 1519. It would appear that the latter date must be accepted, but that the earlier one cannot be determined with certainty.

From Hauser's description of the specimen and from his illustration, it appears that the changes in the skull were probably produced by syphilis (fig. 17).

The lesion was chiefly of the frontal bone and was confined to the outer surface. It consisted of irregular areas of destruction of bone, with new growth of ivory-like bone and some formation of stellate scars, which Hauser believed could have been produced only by syphilitic caries following gummatous periostitis. Hauser found in the Pathological Institute at Erlangen a recent specimen of syphilis of the skull that resembled the Nuremberg skull in all details. He also stated that the syphilitic skulls described by Jäger, referred to on the pages just preceding, were the only other ancient syphilitic skulls from Germany described in the literature.

(To be Concluded)

(p. 931)

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—Ernst Friedberger, director of the Forschungs-Institut für Hygiene und Immunitätslehre in Berlin-Dahlem, outstanding teacher and investigator in the field of immunology and an editor of *Zeitschrift für Immunitätsforschung und experimentelle Therapie* since its beginning, has died at the age of 57.

Ward J. MacNeal has been appointed professor of pathology and bacteriology in the faculty of the New York Post-Graduate Medical School and Hospital of Columbia University.

It is announced that the chair of medicine in the College of France, made vacant by the retirement of Professor D'Arsonval has been filled by the appointment of Charles Nicolle, director of the Pasteur Institute of Tunis and recipient of the Nobel Prize in medicine for 1928 for his work on typhus fever.

Milton C. Winternitz, dean and professor of pathology in the school of medicine of Yale University, has been awarded the Jenkins medal for meritorious service to the dental profession by the Connecticut State Dental Association.

Society News.—The Buffalo Pathological Society has been organized with Kornel Terplan as president and William Jacobs as secretary.

At its recent meeting in Philadelphia the American Association of Immunologists elected A. B. Wadsworth president and Arthur F. Coca secretary-treasurer.

The recently elected officers of the American Association for Cancer Research are: president, E. B. Krumbhaar; vice-president, Ward J. MacNeal; secretary-treasurer, William H. Woglom.

G. R. Callender has been elected president, Victor C. Jacobsen vice-president and Maude E. Abbott secretary-treasurer of the American and Canadian Section of the International Association of Medical Museums.

Abstracts from Current Literature

Pathologic Anatomy

A Rare Osseous Dystrophy (Morquio). Herman F. Meyer and Joseph Brennemann, Am. J. Dis. Child. **43**:123, 1932.

A child is described, with a peculiar, gross, generalized bodily deformity complex that is unique in our experience. We have been able to find only one report in the literature of an apparently identical condition. The essential pathologic change is osseous dystrophy involving practically the whole skeleton except the head, in which achondroplasia is an important factor. We believe that the condition is a definite, uniform clinical entity, that is, *sui generis*, and we hope that this view may be confirmed or refuted in the experience of others.

Authors' Summary.

Hodgkin's Disease of Bone Marrow and Spleen Without Apparent Involvement of Lymph Nodes. E. B. Krumbhaar, Am. J. M. Sc. **182**: 764, 1931.

A fatal case of Hodgkin's disease with autopsy is reported that was practically limited to the spleen and bone marrow, though in these two organs the involvement was extensive. The histologic appearance of the femoral [marrow] suggested that the disease process might have been primary in this tissue. No involvement of lymph nodes could be found, and the lymphoid tissue of the gastrointestinal tract was histologically unchanged. While this does not constitute unequivocal proof of the absence of involvement of the lymph nodes, it points strongly in this direction; while the absence of lesions in the mucosae and of the so-called germinal centers in the spleen suggests interesting speculations as to the type of cell (reticular or endothelial) in which the disease process originates. It is suggested that the disease should be considered a disease of the hematopoietic or of the reticulo-endothelial system rather than of lymphoid tissue.

Author's Summary.

Myeloid Cell Hyperplasia of the Bone Marrow in Agranulocytic Angina. Thomas Fitz-Hugh and E. B. Krumbhaar, Am. J. M. Sc. **183**: 104, 1932.

Myelocytes and myeloblasts were found in the bone marrow at necropsy in more than normal numbers in a case of typical "agranulocytic angina" the antemortem blood count in which was 200 white cells per cubic millimeter (all lymphocytes); i. e., a marked absolute reduction of lymphocytes and absence of all other white cells. Based on this and similar cases recorded in the literature, objection is raised to the current hypothesis of "granulocytic aplasia" as constituting the "primary" pathologic mechanism of the disease, and in its place a hypothesis of "maturation arrest" is proposed for consideration and future study. As there is an absolute reduction of lymphocytes in the blood stream as well as of neurophils, and on account of certain analogies with pernicious anemia, a designation such as pernicious leukopenia is suggested as preferable to the more widely used names for this disease.

Authors' Summary.

Pulmonary Fibrosis: Experiments of Short Duration. Willis S. Lemon and George M. Higgins, Am. J. M. Sc. **183**:153, 1932.

It seems probably that the fibrosis of the lungs produced in workers exposed to dusty atmospheres, especially those in which fine particles of silica make up

the larger percentage of the dust, is an end-product and represents a progressive defeat of the protective mechanisms of the body. It is never found until the lung fails to rid itself of dust carried out of bronchi by ciliary action or of dust carried through the lung by way of the lymphatic channels. With the breakdown in the carrying mechanisms, the burden of protection is on the phagocytic cell, which, with its load of engulfed material, passes to all parts of the lung and ultimately becomes immobilized in those portions of parenchyma in which lymphatic tissue is abundant. The cells concerned are polymorphonuclear leukocytes, which are the first to appear, to disintegrate and to disappear, and clasmatocytes, which appear later, are extremely active, break up less readily, and may become transformed into fibroblasts. In association with the tissue fibroblasts the clasmatocytes form scar tissue. Finally, fibrosis is the result of the action of substances secreted by the cell on the foreign particles. If a tissue poison results from this chemical action, fibrosis is encouraged, and is progressive, lasting as long as the unaltered irritant remains in the lung.

AUTHORS' SUMMARY.

THE INCIDENCE AND SITUATION OF MYOCARDIAL INFARCTION IN ONE THOUSAND CONSECUTIVE POSTMORTEM EXAMINATIONS. ARLIE R. BARNES and RALPH G. BALL, Am. J. M. Sc. **183**:215, 1932.

In 1,000 unselected consecutive postmortem examinations more or less localized myocardial infarction was recognized grossly in 49 subjects (4.9 per cent). Of 685 subjects 40 years of age or more, 47 (6.86 per cent) presented myocardial infarction. A majority of the subjects who had sustained myocardial infarction had had associated hypertension, as judged by the cardiac weights and the records of blood pressure. Notable preponderance of arteriosclerosis in the left coronary artery over that found in the right was not observed in the hearts in which evidence of infarction was found. Gross myocardial infarction resulting from coronary occlusion was practically confined to the left ventricle. Myocardial infarction was observed in the posterior basal portion of the left ventricle in 24 instances as compared with 28 instances in which infarction involved the apex and anterior portion. More careful pathologic study of the posterior basal portion of the left ventricle is urged in order that infarctions in that region may not be overlooked. In 28 instances, infarction occurred in the region supplied by the anterior descending branch of the left coronary artery, as compared with 20 instances in which it occurred in the region of the left ventricle supplied by the right coronary artery. The designation of the anterior descending branch of the left coronary artery as "the artery of coronary occlusion" is no longer justifiable.

AUTHORS' SUMMARY.

DISSECTING ANEURYSMS. M. D. TYSON, Am. J. Path. **7**:581, 1931.

The development of a dissecting aneurysm of the aorta is apparently dependent on degenerative changes in the medial coat. The underlying cause of the medial change is probably obliteration of a large number of vasa vasorum from arteriosclerosis or from a low grade inflammatory process. The aneurysm begins by a rupture of one or more vasa vasorum into the weakened medial layer, with the formation of a hematoma which splits apart the medial fibers. A tear in the intima of the aorta is not a necessary factor in the formation of a dissecting aneurysm. When intimal tears occur, they are probably secondary to the development of the aneurysm.

AUTHOR'S SUMMARY.

MELANOSIS MUCOSAE APPENDICIS VERMIFORMIS. R. D. LILLIE, Am. J. Path. **7**: 701, 1931.

Melanosis of the appendix resembles essentially the melanosis coli described by Pick and others, and probably often forms a part of that condition. The pigment is probably formed first as fine, uncolored granules in large mononuclear cells immediately beneath the surface epithelium. The pigment-carrying cells appear to

be macrophages and fibroblasts. The average age of patients with pigmented appendixes is slightly greater than that of patients with nonpigmented appendixes. No especially significant differences in incidence were found on segregation according to race, sex or occupation. The great diminution in frequency of melanosis in acute and obliterative appendicitis, while undoubtedly due in part to mucosal destruction, is probably not due entirely to that factor, as nonobliterative, nonulcerative subacute appendicitis shows a similar though less marked decrease in the incidence. Adhesions have no noteworthy influence on the incidence of melanosis; atrophy of lymph follicles is possibly associated with a slight increase, and dilatation is quite definitely correlated with an increased frequency and probably a higher grade of melanosis. The duration of symptoms of chronic appendicitis appears to be definitely greater in melanotic than in nonmelanotic appendixes. It is noteworthy that the frequency of melanosis reported here is greater than it has been stated to be in any other published reports on melanosis coli, and the association with chronic appendicitis with dilatation and of longer than average duration may indicate that such chronic appendicitis provides favorable conditions for increased deposition of the pigment. AUTHOR'S SUMMARY.

MAST MYELOCYTE LEUKEMIA IN A CAT. R. D. LILLIE, Am. J. Path. **7**:713, 1931.

Of some twelve reported or mentioned cases of leukemia in cats, this is the fourth to be recorded as splenic or myelogenous and the first in cats in which basophilic myelocytes have been the predominating cell type. About nine cases of mast myelocyte leukemia have been reported in man. Anatomically, this case presented an enormous enlargement of the spleen, enlargement of the liver and extensive mast myelocyte infiltration of the splenic pulp, mast myelocyte nodules in the liver and distention of hepatic capillaries by blood and large numbers of mast myelocytes. Numbers of mast myelocytes were seen in hepatic and renal veins. The blood, lymph glands and bone marrow were not examined.

AUTHOR'S SUMMARY.

RENAL LESIONS IN THE TOXEMIA OF PREGNANCY. E. T. BELL, Am. J. Path. **8**: 1, 1932.

In fatal cases of eclampsia a characteristic glomerular lesion is found. The glomeruli show marked narrowing of all the capillaries, caused by an increase in thickness of the basement membrane of the capillary, but sometimes by an increase of endothelial cells. One case is reported in which the lesions resulting from an attack of eclampsia seven years before are described. These consist of focal hyaline areas in the glomeruli with partial or complete glomerular obliteration and varying degrees of tubular atrophy. It is shown that a peculiar form of chronic renal disease may result from the eclamptic kidney. In one case of hyperemesis gravidarum, glomerular lesions were found that corresponded entirely to those of typical eclampsia. In three other cases, the glomeruli were normal. A fatty liver without necroses is characteristic of this form of toxemia. When a woman with chronic renal disease becomes pregnant, there is usually an aggravation of all the nephritic symptoms. The condition cannot be distinguished from preeclampsia and eclampsia unless the condition of the kidneys prior to pregnancy is known, or unless there is a definite impairment of renal function. In women with chronic nephritis there is shown no special tendency toward the development of eclampsia during gestation.

AUTHOR'S SUMMARY.

TULAREMIC ENCEPHALITIS WITH COEXISTING TUBERCULOSIS. F. W. HARTMAN, Am. J. Path. **8**:57, 1932.

A case of acute tularemia with diffuse encephalitis and coexisting tuberculosis of the kidney and epididymis is described. The lesions of the brain are readily

seen as areas of yellow necrosis and hemorrhage throughout the base. Microscopically, there is patchy necrosis with infiltration by round, wandering cells and polymorphonuclears.

AUTHOR'S SUMMARY.

THE FREQUENCY OF ANOMALOUS RETICULA (CHIARI NETWORK) IN THE RIGHT ATRIUM OF THE HUMAN HEART. F. C. HELWIG, Am. J. Path. **8**:73, 1932.

Eight cases of Chiari's network are recorded. In the first four cases, severe cardiac lesions were found which were the direct cause of the patient's death. In the last four cases, the findings in the heart, aside from the Chiari network, were negligible, and in none of the entire group could any of the clinical symptoms be ascribed to the network itself. Although so few cases have been reported, such reticula are not particularly rare in the human heart, since they were found to be present in 1.5 per cent of routine autopsies. These structures are easily destroyed by careless manipulation, and no doubt will be found quite often if more care is exercised in removing and opening the heart. They were of no clinical significance in this series of cases.

AUTHOR'S SUMMARY.

SYPHILITIC AORTIC ENDOCARDITIS AND SUPERIMPOSED STREPTOCOCCUS VIRIDANS ENDOCARDITIS. E. B. CRAVEN, Am. J. Path. **8**:81, 1932.

In summary, the opinion that in the case reported here the changes in the aorta and aortic valve were basically syphilitic, with a superimposed bacterial endocarditis, is supported by the following facts: lack of a history of articular rheumatism; a history of primary and secondary syphilitic lesions; a strongly positive Wassermann reaction of the blood; absence of lesions of rheumatic fever in the pericardium, myocardium and mitral valve; large and prominent perivascular infiltrations of the aortic adventitia, composed almost exclusively of small lymphocytes; large aortic vascular medial scars penetrating deeply into the medial coat, with the formation of new vascular channels; an acute exudate composed of fibrin, leukocytes and gram-positive cocci (Streptococcus viridans) on the surface of the aortic valve; identification of Streptococcus viridans not only in a culture of the vegetations on the aortic valve, but also in cultures from the blood.

AUTHOR'S SUMMARY.

FORMATION OF BONE MARROW IN THE SUPRARENAL GLAND. D. C. COLLINS, Am. J. Path. **8**:97, 1932.

Fifteen instances of formation of bone marrow in the suprarenal gland have been collected from the literature, with a compilation of the salient features. They have been classified according to Soos' method. Theories concerning the mechanism of their origin have been discussed. An additional example has been reported from the Mayo Clinic with illustrations of the salient gross and microscopic appearances.

AUTHOR'S SUMMARY.

MULTIPLE INFARCTS AND NECROSES OF THE SPLEEN (FLECKMILZ). G. RAKE, Am. J. Path. **8**:107, 1932.

As far as may be told from examining the changes in the spleen, the sequence of events in the cases described seems to be somewhat as follows: Some toxic or other process leads to endarteritis obliterans of the larger and medium-sized vessels and to a hyaline change of the smaller vessels (arterioles) in the kidneys and spleen. At a later date this process becomes more acute, with fulminant necrosis of the walls of the vessels and obliteration of the medium-sized and smaller arteries by means of thrombi. Meuret came to identical conclusions in regard to the two cases that he studied. Owing to the number of vessels involved, the blood supply to areas of the spleen is shut off or reduced below the minimal amount required for the maintenance of the vitality of the tissues, so that necrosis

occurs. At the same time this exacerbation of the arterial and arteriolar disease seems to coincide, if it is not identical, with the factors that lead finally to the death of the patient. Death therefore results a short time after the onset of the necroses in the spleen, which, for this reason, are mostly fresh and show only very early organization at the margin.

AUTHOR'S SUMMARY.

KÖHLER'S DISEASE OF THE SCAPHOID BONE. C. VELLUDA and M. I. NICHITA, Virchows Arch. f. path. Anat. **276**:548, 1930.

The authors believe Köhler's disease of the tarsal scaphoid bone to be the result of diminished blood supply to the bone. The diminished blood supply may be due to maldevelopment or arrested development of the supplying vessels or to thrombosis or traumatic involvement of the vessels. The arterial supply of the scaphoid bone is through the scaphoid artery, which is a branch of the dorsalis pedis artery. The distribution of the artery was studied in roentgenograms made after arterial injections of bismuth. In five of ten preparations the scaphoid artery did not have any anastomoses before entering the bone. The authors conclude that such an arterial supply would predispose to Köhler's disease.

W. SAPHIR.

LEUKEMIC RETICULO-ENDOTHELIOSIS. H. E. BOCK and K. WIEDE, Virchows Arch. f. path. Anat. **276**:553, 1930.

This is a clinical and pathologic report of a case that ran the typical course of acute leukemia. The leukocyte count increased progressively from 10,000 to 46,000, and there was a rapid increase of monocytes to 85 per cent. The authors accept von Schilling's view that the monocytes are derived from the reticulo-endothelial system. They therefore conclude that their case of monocytic leukemia was an example of leukemic reticulo-endotheliosis.

W. SAPHIR.

THE STRUCTURAL LESIONS OF DIABETIC COMA. I. I. MEDWEDEFF, Virchows Arch. f. path. Anat. **276**:622, 1930.

From examination of nine patients dying in diabetic coma, Medwedeff describes the characteristic changes as glycogenic infiltration of the organs, especially of the liver and kidneys; alterations in the islands of Langerhans, such as fibrosis, atrophy and formation of hypertrophied cells with large, pale nuclei; shrinkage of ganglion cells, distention of perigangliomic lymph spaces, fatty change and nuclear alterations in the vegetative nervous centers (globus pallidus, caudate nucleus and hypothalamus).

W. SAPHIR.

EFFECT OF ROENTGEN IRRADIATION ON CALLUS FORMATION. S. FUKASE, Virchows Arch. f. path. Anat. **277**:69, 1930.

The action of roentgen irradiation on the formation of callus and union was studied experimentally in eighty-four rabbits. The fibula of each side was fractured. The fracture of one leg was irradiated, that of the other being left untreated as a control. Intensive irradiation led to decreased formation of callus and delayed union of the bone. Less intensive irradiation led to diminution in formation of callus and bony union within a shorter period as compared with the control side. The amount of preliminary callus formed was less, and its calcification occurred earlier in the treated than in the untreated fracture. Microscopically, there were increased calcification and diminished vascularization and connective tissue formation.

W. SAPHIR.

ARTERIAL CHANGES DUE TO IRRADIATED STEROL. ALICE SCHIFF, Virchows Arch. f. path. Anat. **278**:62, 1930.

Irradiated oil was administered to cats and rabbits in daily doses of from 0.8 to 4 mg. for periods varying from a few days to four months. Larger doses over a prolonged time caused progressive cachexia and wasting. The arterial changes, which involved primarily the media, were most marked in the aorta. The carotid arteries were more frequently damaged than the iliac. In the cat, the arteries of the heart and lung were involved more often than those of the kidney; in the rabbit, the renal arteries were more susceptible. The earliest change noted was swelling of the ground substance of the media. This was followed by irregularity in the course of the elastic fibrils, granular degeneration of the ground substance, rupture of the collagen fibers, deposition of calcium and histiocytic proliferation. The process may involve the circumference of the vessel or may be limited to localized patches. Slight intimal proliferation and moderate cellular infiltration of the adventitia were occasionally seen. The lesions do not regress or heal spontaneously following cessation of administration of the oil.

O. T. SCHULTZ.

Pathologic Chemistry and Physics

BLOOD LIPASE, DIASTASE AND ESTERASE IN MULTIPLE SCLEROSIS. L. A. CRANDALL, JR., and IAN S. CHERRY, Arch. Neurol. & Psychiat. **27**:367, 1932.

Crandall and Cherry studied the blood of patients suffering from multiple sclerosis for the presence of lipase, esterase and diastase. Seventy-eight per cent of patients with multiple sclerosis show the presence of lipase, as against 76 per cent of controls and 80 per cent of patients with a lesion of the liver. Diastase was found in 47.6 per cent of patients with multiple sclerosis and in 75 per cent of those with disease of the liver, while esterase was present within normal limits.

GEORGE B. HASSIN.

THE NATURE AND ORIGIN OF SYNOVIAL FLUID. D. H. KLING, Arch. Surg. **23**:543, 1931.

Normal synovial fluid in about 95 per cent of the effusions in the joints gives precipitation phenomena with dilute acetic acid, hydrochloric acid and mercuric chloride. These reactions are not found in plasma transudates and exudates in other areas of the body, but they do occur with saliva and egg white. The viscosity of synovial fluid is higher than that of plasma and exudates. The specific gravity is in the range of that of other body fluids. A mucinous substance was prepared from the effusions of synovial membranes, which seems to be responsible for the physical chemical properties of this fluid. Mucinous granules were demonstrated in the active cells.

N. ENZER.

KETONE EXCRETION. J. A. BEHRE, J. Biol. Chem. **92**:679, 1931.

The concentration of acetone and diacetic acid in the urine is normally less than 0.5 mg. per hundred cubic centimeters. The amount excreted is highest during the afternoon and evening. During the night there is a decrease in both the amount and the percentage excreted. A still greater decrease in the percentage concentration occurs during the morning, although the actual amount excreted per hour is greater than at night. The increased amount is associated with an increase in the urinary volume and may represent a "washing out" of substances formed during the night. In the early stages of fasting, an increased excretion of ketone bodies is observed as early as from six to twelve hours after the ingestion of food. The excretion of acetone and diacetic acid by diabetic persons receiving

insulin increases during the night, reaches a maximum in the morning and decreases gradually to a minimum, which occurs during the six hours following the last insulin treatment of the day. The concentration remains above the normal level, even when the excretion of sugar is kept normal by insulin.

E. R. MAIN.

CALCIUM AND PHOSPHORUS INTAKE IN HYPERCALCEMIA AND HYPERPHOSPHATEMIA DUE TO IRRADIATED ERGOSTEROL. J. H. JONES and M. RAPOPORT, J. Biol. Chem. **93**:153, 1931.

The administration of viosterol to dogs maintained on a calcium-free diet produces hypercalcemia. Calcium chloride produces a slight increase in the blood calcium and a more marked effect if viosterol is administered forty-eight hours before. The administration of disodium phosphate produces marked hyperphosphatemia both before and after administration of viosterol. The administration of calcium and phosphorus together, as an aqueous solution of dicalcium phosphate, produces a slight decrease in the calcium and almost no change in the phosphorus content of the blood. Following the administration of viosterol the calcium becomes increased, while the phosphorus level tends to remain constant.

E. R. MAIN.

DIFFUSIBILITY OF THE PROTEINS OF NORMAL AND PATHOLOGIC PLASMA. O. H. GAEBLER, J. Biol. Chem. **93**:467, 1931.

Experiments on the dialysis of plasma proteins with collodion membranes of approximately equal permeability in both directions were without evidence that proteinuria is due to an increase in the diffusibility of the proteins or to the presence of substances increasing the permeability of the membranes.

E. R. MAIN.

CALCIFICATION OF THE TIBIA OF THE [illegible]HILD. L. E. BOCHER and G. H. HANSMANN, J. Biol. Chem. [illegible]

The average percentages of ash and calcium in the dry, fat-free tibias of newly born, normal infants are 44.4 and 16.6, respectively. The inorganic composition of these bones appears to be almost invariant. It was unaffected by large differences in the dietary intake of the mothers.

A. P. LOCKE.

THE RELATION OF HYDROSTATIC PRESSURE TO THE GRADIENT OF CAPILLARY PERMEABILITY. P. D. MCMASTER, S. HUDACK and P. ROUS, J. Exper. Med. **55**:203, 1932.

The gradient of permeability along the capillaries of voluntary muscle and the capillaries and venules of skin exists independently of the hydrostatic conditions, though influenced by them. Its presence cannot be explained by a graded tonic contraction of the capillaries. The evidence, like that of previous papers, points to local differences in the barrier offered by the walls of these vessels as responsible for the gradient.

AUTHORS' SUMMARY.

BIOLOGIC ACTION OF ULTRAHIGH FREQUENCY CURRENTS. W. T. SZYMANOWSKI and R. A. HICKS, J. Infect. Dis. **50**:1, 1932.

Ultrahigh frequency irradiation under the described conditions is capable of producing definite attenuation of the three major bacterial toxins, diphtheria, tetanus and botulinus, in raw broth filtrates. This effect is obtained without the development in the toxin of temperatures that would by themselves affect the potency of the toxin. A tentative theory is advanced pertaining to the mechanism of this action.

AUTHORS' SUMMARY.

ADSORPTION OF TUBERCULIN BY COAL DUST. S. LYLE CUMMINS and C. WEATHERALL, J. Hyg. **31**:464, 1931.

Anthracite coal dust is capable of adsorbing the active principle of tuberculin. This power of adsorption is especially well marked when the contact between the coal dust and the tuberculin is brought about in a slightly alkaline medium. Previous saturation with serum proteid, while it appears to diminish, does not annul the power of coal dust to adsorb the active principle of tuberculin.

AUTHORS' SUMMARY.

MALARIAL PIGMENT. F. ROCCHI, Arch. ital. di anat. e istol. pat. **1**:613, 1930.

Malarial pigment was obtained from the spleen by Warasi's method. The pigment was soluble in normal human plasma, in which clotting was prevented by the addition of hirudin. The pigment itself, as well as its ash, gave the iron reaction by Seyfarth's method, which suggests a hematogenous origin.

G. PATRASSI.

MICRODETERMINATION OF LECITHIN IN BLOOD AND PLASMA. W. LINTZEL and G. MONASTERIO, Biochem. Ztschr. **241**:273, 1931.

A method for the determination of lecithin from 10 cc. of blood or plasma is described which is based on the determination of the choline bound to the phosphatide, and which is accomplished by the titration of the trimethylamine freed from this compound. The lecithin content of the plasma is always somewhat lower than that of the total blood. The lecithin content of human blood varies from 0.165 to 0.148 mg. per hundred cubic centimeters, and that of plasma, from 0.141 to 0.121 mg. per hundred cubic centimeters. Sphingomyeline is included in the licithin figure, but the error from this is small, because sphingomyeline occurs in negligible amounts in the blood.

WILHELM C. HUEPER.

IODINE AND BROMINE CO[illegible] THE THYROID GLAND. F. TANINO, Biochem. Ztschr. **241**:392, 1[illegible]

The water in thyroid [illegible]ands with little colloid is considerably more than in glands with moderate or [illegible]h colloid. The ratio of bromine to iodine is increased in thyroid glands containing much colloid (quotient from 16.2 to 15.7) over that in glands with a small amount of colloid (quotient 8.3). The glands from exophthalmic goiters treated with iodine and often with bromine before removal show a low bromine and a high iodine content (quotient below 1). The accumulation of iodine in the gland counteracts apparently the storage of bromine. Examination of the colloidal material gave markedly varying values of iodine and bromine. It appears certain that the high bromine-iodine quotient in thyroid glands with much colloid does not depend on the amount of these substances present in the colloid.

WILHELM C. HUEPER.

CHANGES PRODUCED IN THE REDUCING SUBSTANCES OF THE BLOOD BY IRRADIATION. SOITIRO YOKOTA, Biochem. Ztschr. **241**:398, 1931.

The amount of reducing substances in the blood is changed by irradiation. By the method of Salkowski the blood sugar proper was separated from the other reducing substances. In animals irradiated with ultraviolet rays, a decrease in the amount of reducing substances not precipitable by copper-calcium treatment and a relative increase of the precipitable ones were observed. This cannot be due to changes in the glycophosphates. But, as the amount of phosphorus decreased proportionally more in the filtrate after irradiation than in the blood after irradia-

tion, other phosphorus containing substances must be responsible for the changes observed. Under the effect of irradiation an increase of the phosphorus containing substances precipitable by the copper-calcium treatment occurred.

WILHELM C. HUEPER.

THE INFLUENCE OF INFECTIOUS PROCESSES ON THE PERMEABILITY OF ERYTHROCYTES. M. N. FISCHER and E. A. WOLKOWA, Frankfurt. Ztschr. f. Path. **41**:285, 1931.

The authors examined the permeability of ions within the erythrocytes in a case of typhoid fever. They summarize their findings as follows: The ions of the inorganic ionically dispersed crystalloids diffuse in and out of the erythrocytes. In this process, the Donnan equilibrium of the ions between the red blood cells and the plasma that is normally present is changed in such a manner that the equilibrium constant at the corresponding p_H concentration is smaller than under normal conditions. There occurs a diffusion of the Na^+, H^+ and HCO^-_3 ions into the inside of the erythrocytes and of the Cl^- ions out of the erythrocytes, with a loss of alkaline reserve (of the bicarbonates) in the plasma. These are synergetic processes, which tend to keep the hydrogen ion concentration constant. Considerable changes in the amounts of sugar and "rest" nitrogen within the erythrocytes cannot be explained by the authors and call for further research.

O. SAPHIR.

POSTMORTEM CHANGES IN SPINAL FLUID. S. SÜMEGI and L. FINDEISEN, Frankfurt. Ztschr. f. Path. **41**:431, 1931.

The colloid reaction of the spinal fluid removed post mortem reveals a normal curve until about nine hours after death. Later, the precipitation zone shifts to the acid side. A few hours after death, there is an increase of the protein and nonprotein nitrogen content of the spinal fluid. The albumin-globulin ratio is smaller than normal. Dextrose can be demonstrated in the spinal fluid a few hours after death. The p_H of the spinal fluid shifts very soon toward the acid side.

O. SAPHIR.

EFFECT OF EPINEPHRINE ON THE IODINE CONCENTRATION OF THE BLOOD. A. SCHITTENHELM and B. EISLER, Klin. Wchnschr. **11**:9, 1932.

On intravenous injection of epinephrine hydrochloride there is a sudden increase of iodine in the blood in normal adults and in patients with myxedema. On injection of epinephrine hydrochloride into patients with exophthalmic goiter, in whom there is a high concentration of iodine in the blood, the iodine drops below normal. Explanation of these reactions is not offered.

EDWIN F. HIRSCH.

QUANTITATIVE DETERMINATION OF COPPER IN TISSUES. E. CHERBULIEZ and S. ANSBACHER, Virchows Arch. f. path. Anat. **278**:365, 1930.

The authors give a succinct description of a titrimetric method for the determination of copper in animal tissues and organs. They claim that the method will detect 0.001 mg. of copper, and that it is accurate to within plus or minus 0.0005 mg.

O. T. SCHULTZ.

THE ELECTRICAL CHARGE OF LEUKOCYTES IN INFLAMED TISSUES. A. D. ADO, Ztschr. f. d. ges. exper. Med. **79**:752, 1931.

Leukocytes always retain their negative charge after their entrance into inflamed tissues. The height of the potential of the leukocytes in an exudate is much lower than that of the leukocytes in the circulating blood, and their rapidity of electrical discharge is less. When leukocytes taken from exudates are dispersed

in another medium, such as blood serum, physiologic solution of sodium chloride, etc., their electrical potential is decreased in the same degree as that of leukocytes in the circulating blood. Phagocytic leukocytes have a lower electrical potential than normal ones from the blood.

AUTHOR'S SUMMARY.

THE CHANGES IN BLOOD VOLUME IN EXPERIMENTAL SHOCK. W. GRUNKE and W. HARING, Ztschr. f. d. ges. exper. Med. **79**:763, 1931.

The usefulness of the dye method for the determination of blood volume in conditions of circulatory collapse has been proved in a series of experiments on dogs. It was determined that although the distribution of the dye in various parts of the circulatory system is approximately the same, the concentration of the dye in the blood falls more rapidly in a condition of shock than in normal blood. Determinations of the blood volume in rabbits in shock showed a diminution of from 30 to 50 per cent below the normal. The lessening of the blood volume in the shock induced by diphtheria toxin varied between 1.1 and 15.2 per cent. Only in one case did the volume fall as much as 31.2 per cent. To explain the results of the latter experiments the authors declare that it is not so much a matter of central or peripheral vasodilatation as it is of changes in the heart action.

AUTHORS' SUMMARY.

SURFACE TENSION OF BLOOD SERUM. WALTER SAUER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:450, 1931.

The surface tension of serums from patients with various manifestations of syphilis showed no characteristic differences from the normal. The previously reported lowering of the tension in persons older than 50 years could not be confirmed, but lowering was constant in inactivated and hemolized serums. Repeated estimations of surface tension in the same samples of normal serums gave constant readings, while marked variations were observed in samples of serum from patients suffering from mental diseases. The ring method of Brinkman was employed.

I. DAVIDSOHN.

ANTIRACHITIC VITAMIN FROM IRRADIATED ERGOSTEROL. A. WINDAUS and A. LUETTINGHAUS, Ztschr. f. physiol. Chem. **203**:70, 1931.

Two antirachitic, highly effective compounds, vitamins D_1 and D_2, were isolated in crystalline form from the irradiation products of ergosterol. The vitamin D_1 was obtained in from 30 to 40 per cent by irradiation of ergosterol through a uviolglass filter, which is penetrated by rays above 290 millimicrons. The vitamin D_2 was isolated by Linsert in magnesium spark preparations, yielding up to 30 per cent of the irradiated substance as vitamin D_2. The vitamins D are isomeres of ergosterol. They are very stable over many months, if they do not come in contact with air. Both vitamins are toxic, if given in excessive amounts.

WILHELM C. HUEPER.

Microbiology and Parasitology

ELECTROPHORESIS OF ORGANISMS BELONGING TO THE PNEUMOCOCCUS AND DIPHTHERIA GROUPS. RANDALL L. THOMPSON, Am. J. Hyg. **14**:235 and 244, 1931.

No relationship was found to exist between the virulence of a pneumococcus strain for white mice and the electrophoretic rate of migration of that strain. The electrophoretic rate of migration of the three pneumococcal types decreases in the order: III, I and II. Most strains of organisms belonging to the pneumococcus group may be included in one of three large electrophoretic groups. The existence of two other such groups has been suggested; one of these has not been shown to be definitely distinct from one of the first groups, and the second contains

an insufficient number of members to be significant. All typical strains of any one serologic type of pneumococcus probably belong to the same electrophoretic group. However, one electrophoretic group may include strains not classified in the same serologic category. Rough strains of pneumococcus may or may not migrate more slowly in the electric field than their parent or other strains of the same type as the one from which they were derived.

Both the Abramson and Mudd electrophoresis assemblies were found to give reliable results in the electrophoresis of diphtheria bacilli. The results derived from a study of 173 cultures belonging to the diphtheria group of organisms indicate that toxigenic and nontoxigenic cultures may generally be separated by the method of electrophoresis. The toxigenic organisms migrated more slowly than the nontoxigenic organisms.

AUTHOR'S SUMMARIES.

EARLY LESIONS OF AMOEBIASIS IN MAN, MONKEYS AND CATS. H. L. RATCLIFFE, Am. J. Hyg. **14**:337, 1931.

A comparison of the lesions in monkeys with those described in human intestinal amebiasis shows that they are similar and probably originate in much the same way. The presence of amebas deep in the tissues of man may be accounted for by postmortem invasion, since descriptions are made from tissue fixed several hours after death. The lesions of intestinal amebiasis in the cat do not appear to be comparable to those in primates. In the cat, the pathologic process is one of direct invasion and destruction of the wall of the intestines by the amebas. This is usually accompanied by an inflammatory reaction of the whole wall, indicating bacterial as well as amebic action. True undermining ulcers, comparable to those in primates, probably do not occur, and lesions presented as such seem to have another explanation.

FROM AUTHOR'S SUMMARY.

EXPERIMENTAL TRANSMISSION OF EPIZOOTIC FOX ENCEPHALITIS. R. G. GREEN, N. R. ZIEGLER, E. T. DEWEY and J. E. SHILLINGER, Am. J. Hyg. **14**:353, 1931.

Epizootic encephalitis of foxes has been transmitted to experimental animals from foxes dying during epizootics occurring in two successive years in the Fromm fur ranges. The inoculation of brain and spinal cord virus by cistern puncture into foxes raised under quarantine conditions has been found to be a successful means of maintaining the encephalitis virus. In the experiments here reported, virus stored in 50 per cent glycerin for five and a half months appears to have the same pathogenic properties as does fresh virus. Intramuscular injection of brain virus appears to transmit the disease almost as uniformly as does inoculation by cistern puncture. The spleen of a fox dying of the experimental disease is very active in transmitting the infection to young foxes by cistern puncture. The disease has also been transmitted by the injection of spleen virus into the peritoneal cavity. The virus has been demonstrated in the heart blood of a fox dying of the experimental infection. We have failed to transmit the disease to five foxes by corneal scarification, even though the scarification was thorough and an experimental virus known to be virulent was used. The disease has also been transmitted to young experimental foxes by skin scarification, by intratesticular injection and by inoculation into the nasal cavity. While the mortality of the natural disease seldom appears to exceed 20 per cent of those exposed, the mortality of experimentally inoculated young foxes is approximately 70 per cent.

AUTHORS' SUMMARY.

AVIAN TUBERCULOSIS IN NORMAL AND VACCINATED RABBITS. E. M. MEDLAR, Am. J. Path. **7**:475, 1931.

There is a significant difference in the gross pathology and in the histopathology of nonvaccinated and vaccinated rabbits intravenously inoculated with virulent

avian tubercle bacilli. The textbook description of the tubercle — "a collection of epithelioid cells set in a reticulum with a giant cell in the center and a tendency to undergo caseation" — represents a retrogressive, not a progressive, phase of the pathology of tuberculosis. There is a striking difference in the leukocytic reaction of nonvaccinated and vaccinated rabbits intravenously infected with virulent avian tubercle bacilli. The leukocytic response in the vaccinated rabbits simulates very closely the leukocytic reaction we have observed in human beings who have progressive tuberculosis. This reaction is not specific for tuberculosis, but is caused by unmixed tubercle bacillus infection. The megacaryocyte plays an important rôle in acute avian tuberculosis in the rabbit. What the real significance of the participation of the megacaryocyte in acute tuberculosis is cannot be stated at present.

AUTHOR'S SUMMARY.

LESIONS SUGGESTIVE OF HODGKIN'S DISEASE IN TUBERCULOSIS. E. M. MEDLAR and K. T. SASANO, Am. J. Path. **7**:491, 1931.

Lesions resembling Hodgkin's disease are often present in acute tuberculous foci. These lesions are simply the accumulation of megacaryocytes that have emigrated from the bone marrow to the areas of damaged tissue. They are not true Hodgkin's lesions. The participation of the megacaryocyte in an acute tuberculous process is emphasized. This is not specific for tuberculosis since it occurs in other pathologic conditions. The necessity of exercising care in the diagnosing of Hodgkin's disease from tissue sections is stressed. The presence of the Sternberg type of giant cell in tissue is not sufficient evidence to warrant a diagnosis of Hodgkin's disease. Various types of virulent tubercle bacilli cause the production of the lesions that simulate Hodgkin's disease. This would seem to preclude the possibility that any one type of tubercle bacillus is the etiologic agent of Hodgkin's disease. Lesions suggestive of Hodgkin's disease have been observed only in acute tuberculosis. In chronic tuberculosis these lesions have not been encountered.

AUTHORS' SUMMARY.

THE DENTAL ANLAGE IN CONGENITAL SYPHILIS. T. J. HILL, Am. J. Path. **7**:515, 1931.

The characteristic congenital syphilitic dental deformities are not the direct result of the invasion of the enamel organ by Treponema pallidum.

AUTHOR'S SUMMARY.

INFECTION OF MONKEYS WITH GRANULOMA INGUINALE. W. A. DEMONBREUN and E. W. GOODPASTURE, Am. J. Trop. Med. **11**:311, 1931.

Three Macacus rhesus monkeys inoculated with Donovan organisms from a case of granuloma inguinale showed evidence of an abortive infection with this agent. A biologic method is thus afforded for testing any micro-organism that might be cultivated from these lesions and suspected of being the etiologic agent.

AUTHORS' SUMMARY.

THE PATHOGENIC ACTION OF FILTRATES OF CULTURES OF TUBERCLE BACILLI IN GUINEA PIGS. MAX PINNER and M. VOLDRICH, Am. Rev. Tuberc. **24**:73, 1931.

Filtrable forms of the tubercle bacillus are not demonstrable in pure cultures of tubercle bacilli under the stated conditions; their existence has not been proved in a convincing manner. Broth-culture filtrates from tubercle bacilli cause a characteristic disease in guinea-pigs (marked by rapid loss of weight, dehydration and loss of tissue tone without local lesions). The nosogenic agent of this disease is not a living virus, because (1) it is not present in whole cultures of tubercle

bacilli, grown on solid mediums; (2) it is thermostabile, and (3) it is not transmissible by animal passage. This disease is probably caused by a specific tuberculotoxic substance that may be identical with tuberculin.

AUTHORS' CONCLUSIONS.

TUBERCULOSIS OF THE STOMACH. R. W. GOOD, Arch. Surg. **22**:415, 1931.

The genesis of tuberculosis of the stomach is not settled. Ulcer is the common lesion. Abscesses may form and burrow through the wall. Regional lymph nodes are usually involved. The coincidence of gastric carcinoma and tuberculosis is rare. About twenty-six cases have been collected from the literature. Over half of the cases are associated with tuberculosis elsewhere in the body. It is usually mistaken for carcinoma.

N. ENZER.

THE DERIVATION OF ENCAPSULATED FORMS FROM NON-ENCAPSULATED HEMOLYTIC STREPTOCOCCI. F. B. JENNINGS, JR., Bull. Johns Hopkins Hosp. **49**: 94, 1931.

Seven strains of nonencapsulated hemolytic streptococci, including erysipelas and scarlet fever strains, have been dissociated, in vitro, to encapsulated forms. It seems probable that the potentiality to form capsules may be a characteristic of hemolytic streptococci in general. Dissociation to the encapsulated form enhances the culture's virulence for mice to a high degree. The encapsulated forms have retained their morphology and virulence, without animal passage (in vitro) since their dissociation—a period which has been from one to three years.

AUTHOR'S SUMMARY.

THE RAT FLEA AS VECTOR OF TYPHUS FEVER. H. A. KEMP, J. A. M. A. **97**: 775, 1931.

Guinea-pigs inoculated with fleas removed from rats that had been trapped at a typhus focus developed lesions characteristic of endemic typhus fever. Animals recovered from an attack produced by this virus were found to be immune to a strain of typhus virus established from the blood of a human patient with endemic typhus. Animals that were immune to blood virus were immune to the strain of rat flea virus established by guinea-pig inoculation.

AUTHOR'S SUMMARY.

CULTIVATION OF RICKETTSIA-LIKE MICROORGANISMS FROM CERTAIN BLOOD-SUCKING PUPIPARA. I. J. KLIGLER and M. ASCHNER, J. Bact. **22**:103, 1931.

Experiments are reported dealing with the cultivation of extracellular nonpathogenic rickettsias from a number of pupipara. Methods are described by means of which cultures of Rickettsia were obtained repeatedly from the parasitic pupipara of the sheep, goat, horse and dog. The organisms obtained in culture were minute, gram-negative, coccoid rods corresponding to the usual description of Rickettsia and resembling the forms seen in the intestines of the insects.

AUTHORS' SUMMARY.

THE RECOVERY OF BACTERIOPHAGE FROM FILTRATES OF HEATED SPORE-SUSPENSIONS. P. B. COWLES, J. Bact. **22**:119, 1931.

That bacteriophage may be demonstrated in growth resulting from spores that have been heated to a much higher temperature than that tolerated by free bacteriophage was shown by den Dooren de Jong, who on this basis concluded that the lytic principle was generated in the cell. In this paper evidence is presented to show that known bacteriophage-free strains of several spore-forming

organisms may be so changed by the action of the bacteriophage that the principle can be demonstrated in filtrates of cultures developed from heated spores. This does not necessarily mean that the lytic agent as such survives the heating process, but it does mean that the recovery of a lytic principle from a pasteurized culture is not conclusive proof of the spontaneous generation of bacteriophage.

AUTHOR'S SUMMARY.

THE BEHAVIOR OF ACID-FAST BACTERIA IN OIL AND WATER SYSTEMS. B. G. REED and C. E. RICE, J. Bact. **22**:239, 1931.

On shaking watery suspensions of acid-fast bacteria with oil, they readily pass into the oil, while nonacid-fast bacteria remain in the water. The same reaction occurs with a variety of fat solvents. The partition into oil is shown quantitatively to be nearly complete for tubercle bacilli and from 70 to 90 per cent for six other acid-fast species. Homologous immune serum inhibits, in proportion to its concentration, the partition from water to oil. Emulsifying agents such as gelatin and sodium oleate have a similar effect.

AUTHORS' SUMMARY.

THE ELECTRICAL CHARGE OF BACTERIOPHAGE. C. E. CLIFTON and R. R. MADISON, J. Bact. **22**:255, 1931.

The electrical charge carried by the bacteriophage was determined by noting the tendency of this agent to climb with water in blotting paper. The results presented herein indicate that the iso-electric point of the anticoli bacteriophage tested is around p_H 2.9; of antishiga bacteriophage, near p_H 3.1; of antistaphylococcus bacteriophage, approximately at p_H 3.5, and of antipyocyaneus bacteriophage, below a p_H of 2.1.

AUTHORS' SUMMARY.

TULAREMIA IN NORWAY. TH. THJØTTA, J. Infect. Dis. **49**:99, 1931.

Tularemia is not a rare disease in Norway. It has been found over nearly the whole country. With the exception of the typhoidal type of the disease, all other types have been encountered. No deaths have been seen. Besides the hare, the lemming is probably a carrier. No case originating from the bite of an insect has been seen as yet.

AUTHOR'S SUMMARY.

BRUCELLA ABORTUS. W. N. PLASTRIDGE and J. G. MCALPINE, J. Infect. Dis. **49**:127, 1931.

One hundred and thirty-six strains of Br. abortus of bovine, porcine and equine origin were identified by the dextrose utilization method of McAlpine and Slanetz, and by Huddleson's dye plate method. Eight of sixty strains of bovine origin isolated in the United States were found to be of the porcine, and fifty-two of the bovine, type. Of fifty strains of bovine origin isolated in Europe, forty-eight were found to be of the bovine type, while two appeared to be of intermediate types. All of the twenty-two strains of Br. abortus of porcine origin utilized appreciable amounts of dextrose and behaved as the porcine type on the dye plates. Four strains of equine origin proved to be of the bovine type of Br. abortus.

AUTHORS' SUMMARY.

THE HERROLD EGG YOLK AGAR MEDIUM IN THE DIAGNOSIS OF TUBERCULOSIS. C. I. WOOLSEY, J. Infect. Dis. **49**:177, 1931.

One egg yolk added to 200 cc. of 1.5 per cent agar at 60 C., mixed well, makes a valuable medium. The results of cultures on this medium (Herrold) and of inoculations into guinea-pigs agreed in 93 per cent of 130 cases; in 5 of the 9 cases in which the results disagree, the Herrold cultures were found the more reliable. Thirty-six strains of tubercle bacilli were recovered on the Herrold

medium in an average of 12.2 days. Mixing freshly aspirated fluids from tuberculous processes with an equal amount of 20 per cent sodium citrate solution prevents coagulation. However, the entire coagulum may be placed on the Herrold medium and growths of tubercle bacilli obtained in that way.

AUTHOR'S SUMMARY.

HERPETIC VIRUS IN MICE. H. B. ANDERVONT, J. Infect. Dis. **49**:507, 1931.

Continued passage of the herpetic virus through the brains of mice did not increase its pathogenicity for rabbits. Male mice appear to be more susceptible to cutaneous inoculation of the JB virus, and there is also evidence of seasonal variation in the susceptibility of the mice. Nitric acid and formaldehyde destroy the JB virus when applied to the infected skin. Practically all mice showing a local reaction after injection of the JB virus into the abdominal skin develop encephalitis, but many survive after cutaneous inoculation of the tail. These tail-inoculated mice are immune after three days to further cutaneous or intracranial inoculation of JB virus. Mice can also be immunized by intraperitoneal injections of formaldehydized suspensions of brain infected with JB virus.

FROM AUTHOR'S SUMMARY.

INTERSTITIAL PERIPHERAL NEURITIS IN EXPERIMENTAL POLIOMYELITIS. A. JORDI, J. Infect. Dis. **49**:530, 1931.

The peripheral nerves in seventeen of twenty monkeys that were infected experimentally by intracerebral and intranasal methods showed a definite interstitial inflammation. The perivascular infiltrations, mostly by round cells, were generally small and inconspicuous and were not numerous. Infiltrations were found as early as twelve hours after the onset of paralysis. However, in the three animals the nerves of which were free from infiltrations and in a few animals in which not all the extremities were affected, paralysis had existed for less than six days. Infiltrations were present in the nerves of the extremities that were not paralyzed. The sciatic nerves of one normal monkey which were partly cut, respectively, twelve and four days before the animal was killed showed secondary degeneration, but no signs of interstitial inflammation, thus proving that the interstitial neuritis in experimental poliomyelitis is caused by the specific virus. In early stages of poliomyelitis, necrosis of the ganglion cells, both in the spinal cord and in the intervertebral ganglion cells, and not the interstitial inflammation, is the first manifestation of the virus.

AUTHOR'S SUMMARY.

RELATION BETWEEN BACTERIA AND TEMPERATURE IN SUBACUTE BACTERIAL ENDOCARDITIS. H. WEISS and R. OTTENBERG, J. Infect. Dis. **50**:61, 1932.

The relationship of the temperature to the bacteremia in four cases of subacute bacterial endocarditis indicates that a correlation between these two phenomena probably exists. The bacteremia is apparently maintained (1) by a constant, practically uniform feeding of bacteria into the blood stream from the endocardial vegetations and (2) by the sudden liberation of a large number of organisms. The bacteremia in each case apparently establishes a balance between bacterial invasion and immunologic response, which it maintains throughout the course of the disease. The clinical severity of the disease bears no relationship to the degree of bacteremia. The results indicate that if diagnostic blood cultures, usually made at the time of hyperpyrexia, are made just before the expected rise in temperature, more positive results and higher bacterial counts will be obtained.

AUTHORS' SUMMARY.

DIPHTHEROIDS IN BLOOD CULTURES. L. THOMPSON, J. Infect. Dis. **50**:69, 1932.

Of 1,079 blood cultures, 33 (3 per cent) gave a growth of diphtheroids. Study of 17 strains disclosed great variation among the organisms in regard to morpho-

logic and cultural characteristics. It was not possible to correlate the finding of diphtheroids in the blood cultures with the clinical diagnosis. In none of the cultures studied was any marked change from the morphology of the diphtheroids noted. An instance is cited in which a pleomorphic streptococcus was obtained from the blood in a case of subacute bacterial endocarditis. Diphtheroids appear to have the same significance in blood cultures as the saprophytic cocci.

AUTHOR'S SUMMARY.

CHARACTERISTICS OF MONILIA FROM HUMAN SOURCES. W. D. STOVALL and A. A. BUBOLZ, J. Infect. Dis. **50**:73, 1932.

One hundred and fifty cultures of Monilia isolated from cases of bronchitis, vaginitis and thrush and ten secured from the American Type Culture Collection were studied. By morphology of colonies, fermentation of carbohydrates and behavior toward milk all cultures were classified into three species. Two species were represented in type cultures, M. albicans, type II, and M. candida, type III. One species, Type I, was rarely found associated with human disease. M. albicans was isolated more frequently than M. candida. The authors conclude that many cultures of Monilia described as different species really belong to these two types. The cultural and biochemical characteristics were remarkably constant, and the reported variability is thought to be due to a lack of uniformity in technic.

EDNA DELVES.

METABOLIC STUDIES OF STREPTOCOCCI. M. A. FARRELL and S. THOMAS, J. Infect. Dis. **50**:134, 1932.

Nitrogen supplied in the form of ammonium salts, asparagine and uric acid failed to stimulate or support the growth of S. rheumaticus. When rhamnose, levulose or galactose was added to a nonprotein source of nitrogen, growth was secured to the third transplant. When the nonprotein nitrogen was enriched with an additional source of nitrogen in the form of an amino-acid, no growth was obtained. The original inoculum survived in some of the added amino-acids up to forty-eight days, while other amino-acids were antagonistic, the bacteria being destroyed at the end of two days. When any one of the various sugars was added to the amino-acid that was the least inhibitory, no growth resulted. When dextrose was added to each of the nine amino-acids, synthetic mediums being used as substrates, the antagonistic action of tyrosine, tryptophan and phenylalanine was shown to be lessened. S. rheumaticus grew well on milk aminoids.

AUTHORS' SUMMARY.

VARIANTS OF SALMONELLA PULLORUM. W. PLASTRIDGE and L. F. RETTGER, J. Infect. Dis. **50**:146, 1932.

Extracts of the livers and the intestinal contents of adult birds surviving an acute attack of disease due to infection with S. pullorum were found to contain a bacteriophage that was active against the cells of S. pullorum in dilutions including 1×10^{-10}. In the presence of this active principle, cells of S. pullorum in most instances were lysed or became phage-resistant, and in the other instances the development of the cells appeared to parallel the action of the bacteriophage. Under the last-named condition, cells of S. pullorum were inagglutinable by antiserum for the ordinary S. pullorum. Three principal types of colonies were observed on beef infusion and liver infusion agars inoculated with the mixtures of phage and culture; namely, S1 or ordinary smooth colonies of S. pullorum, S2 colonies that were smooth in appearance, but much larger than S1 colonies, and R colonies that possessed distinctly roughened surfaces. Colonies developing on ordinary nutrient agar inoculated with cells from R colonies showed only a slight tendency toward roughness. The morphology, agglutinability and colonial characteristics of substrains of these three types of colonies are discussed.

AUTHORS' SUMMARY.

INTRANUCLEAR INCLUSIONS IN THE SUBMAXILLARY GLAND OF THE RAT. M. J. THOMPSON, J. Infect. Dis. **50**:162, 1932.

Specific inclusions were found within the nuclei of cells in the ducts of the submaxillary gland of the rat. Fourteen per cent of a series of seventy 2 months old rats showed these affected cells. The incidence was suggestive of either a seasonal variation or of an epizootic. The histologic changes in the submaxillary gland of the guinea-pig infected with submaxillary virus have been compared with those in the affected gland of the rat. It is believed that one is dealing with a disease caused by a virus different from that causing the submaxillary condition of the guinea-pig. The submaxillary lesion in the rat possesses features in common with the lesions of other diseases due to viruses.

AUTHOR'S SUMMARY.

CONCERNING THE DISTRIBUTION OF DIPHYLLOBOTHRIUM LATUM IN NORTH AMERICA. T. B. MAGATH and H. E. ESSEX, J. Prev. Med. **5**:227, 1931.

Fish were examined from practically every watershed in Minnesota. Infested fish were found in four lakes, three of which drain by northern passage into Canadian lakes; the fourth drains into Lake Superior. The fish found infested were of the following kinds: Esox lucius, Stizostedion vitreum and Perca flavescens. The following plankton forms were found to be first intermediate hosts for the parasite: Diaptomus oregonensis (previously reported by Essex), Diaptomus sicilis and Diaptomus siciloides. The primary introduction of Diphyllobothrium latum into the waters of North America was made by immigrants accustomed to eat raw fish, who came from the endemic centers of Europe, in particular from the Baltic states, northern Sweden, Denmark, Finland, Lithuania and Germany. Many of these people, particularly the Scandinavians and Finlanders, have settled in the lake regions of central North America, where the smaller lakes contain suitable intermediate hosts to insure the development of the worm. The temperatures at the bottom of the lakes play a part in determining whether the eggs will hatch. In many of the cities and towns of Minnesota and Canada where these infested persons have congregated, raw sewage is emptied into the lakes or streams, and in other towns the sewage systems will not prevent the escape of eggs or coracidia. Moreover, chance contamination of these lakes by man is probably very common, since the people are ardent hunters, fishermen and trappers, as well as lumbermen. The high viability of eggs from human sources increases the hazard. Water connections between the lakes allow fish to migrate and carry infestation to new streams and lakes. From the several fish hatcheries situated in these infested regions fish are transported and planted in many waterways. If the hatchery water is taken from a lake contaminated with Diphyllobothrium latum eggs, the chances are great that the susceptible fish will become infested and carry the infestation when transported to some far removed lake. That animals other than man will carry infestation to the fish of uninfested waters and that the infestation will maintain itself in the new lake is a possibility as yet unproved. No one has positively recorded finding the worm in nature in any wild animal in North America except in the case of one fox. Dogs are readily infested, and many of those in the lake regions harbor the worm, but their part in the spread of the infestation seems at present more hypothetic than practical. In the light of present knowledge the control of infestations by Diphyllobothrium latum lies chiefly in the hands of man.

AUTHORS' SUMMARY.

THE ADSORPTION AND ELUTION OF BACTERIOPHAGE AND FOWL-POX VIRUS. I. J. KLIGLER and L. OLITZKI, Brit. J. Exper. Path. **12**:172, 1931.

Coli bacteriophage and the virus of fowl-pox are completely adsorbed by kaolin and can be partially recovered from the adsorbent by elution with dilute ammonium hydroxide. Chemical tests for proteins in the purified suspension are negative.

C. E. CLIFTON.

Immunology

HUMAN BLOOD IN PROTECTION AGAINST MUMPS. LOUIS H. BARENBERG and JACK OSTROFF, Am. J. Dis. Child. **42**:1109, 1931.

A study was made of 180 children, ranging in age from 1½ to 3 years, and housed in nine separate wards, who were susceptible to mumps. Serotherapy was employed in 55 of these 180 susceptible children in order to reduce the incidence or to attenuate the disease. (At the onset of the epidemic, 44 children received 12 cc. of blood from convalescent patients, and 11 children the same amount of blood from an adult who had had mumps in childhood.) In seven wards, comprising 139 children, prophylactic treatment was given to about half the children in each ward, the rest serving as controls. Those in two other wards were not given specific therapy, and consequently afforded an excellent opportunity for comparison.

The average incidence in the untreated wards was 49.5 per cent, whereas in the other seven wards, in which treatment was given to some of the children, the average incidence was 26.6 per cent. Serotherapy proved of definite value in reducing the incidence of mumps, the average for the treated children being 15 per cent, and that for the untreated children, 39 per cent. Mumps was markedly attenuated by this form of serotherapy.

The results from the injection of blood from an adult who had had mumps in childhood were not as definitely favorable as those from the injection of blood of patients convalescent from mumps, perhaps because inadequate amounts were injected.

A definite shortening of the epidemic was brought about by the use of serotherapy; from a period of about six months in previous epidemics the period dropped to about two months in the present one.

AUTHORS' SUMMARY.

HYPERSENSITIVITY TO BACTERIAL PROTEINS AND ITS RÔLE IN SUSCEPTIBILITY AND IMMUNITY. W. B. WHERRY, Am. J. Hyg. **14**:539, 1931.

Bacteria are potential parasites if they can produce poisons that hydrate the tissues of an animal, thus putting the food substances into solution. Some of the poisons produced might be amines. The fact that bacteria contain poisons capable of hydrating tissues may be determined by the intradermal inoculation of the bacteria, extracts of the bacteria or their toxins, or by immersing tissues in the toxins in the presence of free water. A state of hypersensitivity to bacterial toxins, extracts or heat-killed bacteria may be determined by the intradermal test. Such tests have shown that persons suffering from many infections, including asthma, acute and chronic sinusitis, colds, urticaria, angioneurotic edema, spastic and mucous colitis and chronic arthritis, are hypersensitive to bacterial proteins. These cases can be relieved by desensitization, and this is best brought about by partially detoxicated antigens. Amines and foreign proteins pass the mucosa best in an alkaline medium. Cases showing intoxication or sensitization to proteins derived from the colon show evidences of putrefaction taking place in an alkaline medium. The saccharolytic colonic flora is suppressed in these cases, and the symptoms may be relieved by feeding lactose. Keeping the contents of the colon in an acid state should guard against the development of such types of hypersensitivity.

AUTHOR'S SUMMARY.

THE PRESENCE OF HETEROPHILE ANTIBODIES IN INFECTIOUS MONONUCLEOSIS. JOHN R. PAUL and W. W. BUNNELL, Am. J. M. Sc. **183**:90, 1932.

Heterophile antibodies, demonstrable in the form of sheep cells agglutinins have been recorded in rather high concentrations in the active stages of four cases of infectious mononucleosis. Apart from cases of serum disease, and one notable exception, we have failed to note this in a large series of cases representing a variety of clinical conditions, including Vincent's angina, lymphatic leukemia and

other blood dyscrasias. There would seem to be two possible explanations for this finding: (1) that the unknown agent responsible for infectious mononucleosis contains the heterophile antigen; (2) that we are dealing with an example of the production of iso-agglutinins elicited by abnormal cells, which are present either in the blood or elsewhere during active stages of the disease.

AUTHORS' SUMMARY.

THE NATURE OF ALLERGY IN TUBERCULOSIS AS REVEALED BY TISSUE CULTURE STUDIES. A. R. RICH and M. R. LEWIS, Bull. Johns Hopkins Hosp. **50**:115, 1932.

The washed cells of the allergic, tuberculous body have been shown to retain their hypersensitivity to tuberculin when isolated from the body in tissue cultures. It is therefore clear that circulatory, nervous or other mechanisms dependent on the intact body are not necessary for the production of allergic damage. Cellular injury and necrosis associated with allergy in tuberculosis result from a change in the individual fixed tissue and blood cells, which renders them hypersensitive to the protein of the tubercle bacillus. This change, in all probability, consists in the intimate attachment of antibody to the cells. Free, circulating antibody is not necessary for the production of the immediate, local injurious affects of allergy in tuberculosis.

AUTHORS' SUMMARY.

THE AGGLUTINATION OF BACILLUS SORDELLII AND CLOSTRIDIUM OEDEMATOIDES. I. C. HALL and A. L. SCOTT, J. Bact. **22**:375, 1931.

There is cross-agglutination between all strains of B. sordellii and C. oedematoides. Serum prepared against B. sordellii or against C. oedematoides does not cross-agglutinate B. sporogenes, B. tyrosinogenes or B. novyi. B. sordellii and C. oedematodes are therefore distinct serologically from other species of obligately anaerobic bacilli.

AUTHORS' SUMMARY.

SYPHILITIC BLOOD PROTEINS (SURFACE TENSION AND SOLUBILITY). S. T. WALTON, J. Exper. Med. **54**:859, 1931.

The surface tension of normal blood serum is considerably lowered by standing undisturbed for a period of one hour (time drop). The greatest time drop recorded is with serum diluted approximately 10,000 times in fresh serum or 50,000 times in heated serum. Immune serum is not affected in the same manner by heat as is normal serum. Syphilitic serum and antisheep cell rabbit serum behave similarly in this respect. The albumin of serum is much more readily soluble in alkaline buffer solutions than the globulin is, and globulin from normal serum ionizes more than that from syphilitic serum. Further investigations are being made in an effort to determine why the proteins aggregate or dissociate under the influence of the factors under consideration.

AUTHOR'S SUMMARY.

ORAL IMMUNIZATION AGAINST PNEUMOCOCCUS TYPES II AND III, AND TYPE I. V. ROSS, J. Exper. Med. **54**:875 and 899, 1931.

Older rats survive greater doses of Pneumococcus type II than young ones, showing the acquisition of a partial natural immunity. The same is true with regard to type III, but the immunity appears later in life. An active immunity can be created against types II and III in rats by feeding dead organisms or the Berkefeld filtrate of the bile salt-dissolved cells. This immunity resembles that obtained against type I. Feeding the purified soluble specific substance of type I protects rats against an intraperitoneal injection of the virulent organism. This increased resistance in some ways resembles that obtained when the dead or dissolved bacteria are fed, but the proportion of animals protected and the height of the immunity are not as great. Mice were not protected by immunization with the purified soluble specific substance. A sodium glycocholate solution of type I lost part of its immunizing power after standing one year.

EDNA DELVES.

ORAL IMMUNIZATION WITH SOLUBLE SPECIFIC PNEUMOCOCCAL SUBSTANCE. V. Ross, J. Exper. Med. **55**:1 and 13, 1932.

When the soluble specific substance of Pneumococcus type II was fed to rats, little or no increased resistance to the organism was obtained. When the specific substance of type III was fed, an increased resistance to the virulent organism resulted. The percentage of animals protected is smaller than when the whole or the dissolved cell is fed. When the specific polysaccharide of type I was fed, no immunity against type II or type III was obtained, and the ingestion of the specific substances of types II and III did not protect rats against type I.

Rats, when fed the soluble specific substances of types I, II and III, excrete a very large proportion in the feces. Following ingestion of these substances, tests sensitive enough to detect 1 part in 2,000,000 of serum, and 1 part in 3,000,000 of urine, were negative. The polysaccharide of type I, when recovered from the feces, is as active an immunizing agent as it was originally.

AUTHOR'S SUMMARY.

THE IDENTITY OF TYPE-SPECIFIC AGGLUTININ AND PRECIPITIN REACTIONS WITH PNEUMOCOCCUS. T. FRANCIS, JR., J. Exper. Med. **55**:55, 1932.

The results obtained in the agglutination reaction conform qualitatively with the principles described by Heidelberger and Kendall for the phenomenon of precipitation. They indicate that the essential mechanisms of the two reactions are identical, and that the active reagents are the same in both.

AUTHOR'S SUMMARY.

PRECIPITINOGEN AND PRECIPITINS IN RELATION TO SERUM SICKNESS IN RABBITS. L. JONES and M. S. FLEISHER, J. Exper. Med. **55**:79, 1932.

It has not been possible to demonstrate in rabbits affected with serum sickness any constant temporal relationship between precipitin and precipitinogen in the blood, on one hand, and occurrence of serum sickness, on the other hand. It has not been possible to demonstrate any differences between the precipitin and precipitinogen curves of rabbits in which serum sickness developed and those of rabbits in which it did not develop. There is, therefore, no evidence that the occurrence of serum sickness can be directly associated with the production or the appearance of precipitins.

AUTHORS' SUMMARY.

THE DISAPPEARANCE OF LIVING BACTERIA FROM THE BLOOD STREAM. P. R. CANNON, F. L. SULLIVAN and E. F. NECKERMANN, J. Exper. Med. **55**:121, 1932.

The simultaneous intravenous injection into normal and actively immunized rabbits of equal quantities of living staphylococci or paratyphoid bacilli is followed by a distinctly accelerated rate of removal of the bacteria from the blood streams of the immune animals. This altered reactivity is due essentially to specific active immunization. The bacteria pass rapidly through the capillary bed of the lungs, extracellularly and dispersed for the most part, and become generalized through the blood stream. The bacteria are quickly removed from the circulating blood in the immune animals and less rapidly in the normal ones, by various organs, particularly the liver and spleen, where they accumulate in enormous numbers, become adherent to the lining membrane of the sinusoides of the liver and apparently to the macrophages of the spleen and are phagocytosed by the macrophages and leukocytes in these organs. Associated with this effect are morphologic changes in the bacteria, as shown by swelling, loss of staining power and evidences of increased cohesiveness and decreased viscosity, these changes being apparent as early as two minutes after their intravenous injection. As these changes are not seen to a marked degree within the lungs or other organs, they are probably the result of a local antigen-antibody reaction of a bacteriotropic type in the two

organs generally considered to be most actively concerned with the production of immune bodies. By means of this accelerated bacteriotropic effect in the actively immunized animals, phagocytosis is facilitated and intracellular digestion of the bacteria is enhanced.

AUTHORS' SUMMARY.

LOCAL ANAPHYLACTIC INFLAMMATION IN THE RABBIT PERICARDIUM, HEART, AND AORTA. D. SEEGAL, B. C. SEEGAL and E. L. JOST, J. Exper. Med. **55**:155, 1932.

An intense inflammatory reaction in the pericardium, heart and intrapericardial aorta can regularly be produced in a sensitized rabbit by the intrapericardial injection of the homologous antigen.

AUTHORS' SUMMARY.

LOCAL ANAPHYLACTIC INFLAMMATION IN THE RABBIT BRAIN. L. M. DAVIDOFF, B. C. SEEGAL and D. SEEGAL, J. Exper. Med. **55**:163, 1932.

Sixteen of seventeen rabbits actively sensitized to various antigens by repeated cerebral and intravenous injections showed on intracerebral reinjection of the same antigen local anaphylactic inflammation of the brain at the site of inoculation. Six of twenty rabbits actively sensitized to either horse serum or egg albumin by extracerebral injections showed, on introduction of the homologous antigen into the cerebrum, local anaphylactic inflammation at the site of inoculation. The pathologic picture of Arthus' phenomenon in the brain of the rabbit resembled that seen in the skin, after allowing for differences in the fundamental structure of the tissues involved. None of the control animals exhibited lesions comparable to those found in the experimental animals. A few controls showed slight hemorrhages due to mechanical injury of blood vessels. Clinical symptoms of varying degrees of severity, often leading to the death of rabbit, were observed in the sensitized animals. These symptoms were referable to the site of injection.

AUTHORS' SUMMARY.

IMMUNOLOGICAL REACTIONS OF PNEUMONIC PLEURAL FLUIDS. M. FINLAND, J. Exper. Med. **55**:169, 1932.

Pleuritic exudates from patients with lobar pneumonia may be sterile or infected. Sterile fluids, at or about the time of crisis, contain actively acquired antibodies similar to those in the blood serum. Infected fluids do not contain such antibodies, presumably because of the presence in them of large amounts of soluble specific substance. Sterile fluids from patients treated with immune serum contain both horse serum and antibodies similar to those injected. Infected fluids from serum-treated persons contain horse serum and such heterologous antibodies as were contained in the therapeutic serum together with homologous soluble specific substance. The concentrations of horse serum and antibodies in pneumonic fluids are usually the same or somewhat less than those in corresponding blood serums.

AUTHOR'S SUMMARY.

TOXIN-ANTITOXIN REACTION WITHOUT NEUTRALIZATION. J. FREUND, J. Exper. Med. **55**:181, 1932.

Collodion particles adsorb diphtheria, tetanus and botulinus toxins. These toxins are retained on the particles when washed, but are at least in part released in the animal. The adsorbed toxins are neutralized by adsorption of the corresponding antitoxins, but are unaffected by other serums. When collodion particles are treated first with tetanus antitoxin, then with diphtheria toxin, they are not toxic, but they become toxic when they are treated first with diphtheria antitoxin, then with diphtheria toxin. Similarly when collodion particles are treated first with diphtheria antitoxin and then with tetanus toxin, they do not become toxic, but they become toxic when they are treated with tetanus antitoxin and tetanus toxin.

AUTHOR'S SUMMARY.

SPECIFIC AGGLUTINATION OF PNEUMOCOCCUS TYPES I, II AND III. J. F. ENDERS, J. Exper. Med. **55**:191, 1932.

Type-specific agglutination of Pneumococcus types I, II and III has been demonstrated in antiserums largely deprived of the carbohydrate antibody. The type-specific agglutinogens in Pneumococcus I and II responsible for agglutination in such antiserums are inactivated by heating in alkaline solution at 100 C. The specific carbohydrate remains unaltered under these conditions. The relationship of the type-specific agglutinogen in Pneumococcus I to the type-specific A substance has been discussed. The possible application of these results to the standardization of therapeutic antiserums by agglutinin titer has been discussed. On the basis of the experiments recorded, a tentative explanation is offered for the failure of Pneumococcus type II to absorb the agglutinins from serum prepared against Friedländer's bacillus type B.

AUTHOR'S SUMMARY.

ANTISERUM IN INFLUENZAL MENINGITIS. H. K. WARD and J. WRIGHT, J. Exper. Med. **55**:223, 235, 1932.

Acute purulent meningitis due to invasion of the meninges by Pfeiffer's influenza bacillus is not uncommon in infants and children. The mortality is very high. Complement is entirely lacking in the cerebrospinal fluid in these cases, and bactericidal experiments suggest that the injection of a specific antiserum has but slight lethal effect on the organisms unless complement is injected at the same time. Treatment with a mixture of specific antiserum and complement led in some cases to a definite clinical improvement, coincident with sterilization and clearing of the spinal fluid. But after some days, the patient had a relapse and died. Autopsy showed localized abscesses in the vicinity of the base of the brain, the lesions being definitely walled off from the subarachnoid space. In one case the patient recovered. Since the walls of the abscesses apparently present an insuperable mechanical obstacle to the action of the antiserum and complement, the possibility of preventing the formation of abscesses is discussed. Earlier diagnosis and more rapid sterilization are the most obvious measures. Bactericidal experiments indicate that the proportion of antiserum to complement may be an important factor in bringing about a more rapid elimination of the bacilli.

By a suitable bactericidal technic, it can be demonstrated that the virulent S influenza bacillus is completely resistant to the bactericidal action of diluted normal unheated serum. In contrast, the R organism is easily killed when subjected to diluted normal serum. Although this is not a true test of virulence, it promises to be a useful substitute when a susceptible animal is not available. The filtrate of the S culture contains a substance with a strong antibactericidal effect, but that of the R culture does not contain this substance. It would appear probable that this antibactericidal substance is identical with, or closely related to, the precipitinogen (or soluble substance), which is present only in the culture fluid of the S influenza bacillus. In view of differences in the heat stability of the two substances, this question must remain in doubt until a supply of purified precipitinogen is available. Comparisons of quantitative agglutination, precipitation and bactericidal action between (*a*) R-absorbed anti-S serum and unabsorbed anti-S serum and (*b*) anti-S serum and anti-R serum indicate that the agglutinogen is a separate antigen, and the agglutinin a separate antibody, taking no part in the bactericidal action of the antiserum. They also indicate that the precipitin, which is present only in the anti-S serum, is identical with the bactericidal antibody.

AUTHORS' SUMMARIES.

ANTIGENIC STREPTOCOCCAL HEMOLYSIN. E. W. TODD, J. Exper. Med. **55**:267, 1932.

Normal serum used in cultures for preparation of streptocolysin modifies the properties of the streptocolysin, causing delayed hemolysis, increased filtrability, resistance to oxidation or reduction and absence of antigenicity. Streptocolysin

prepared without serum is an active antigen. Similar temperatures are required to destroy the antigenic activity of serum-free streptocolysin and the intracutaneous reactivity of Dick toxin. Scarlet fever antitoxin contains antistreptocolysin which does not neutralize serum streptocolysin and which can be detected only by titration against serum-free streptocolysin. The antihemolysin which neutralizes serum-free streptocolysin is species-specific but not type-specific.

AUTHOR'S SUMMARY.

THE CORRELATION BETWEEN PROTECTIVE VALUE AND OTHER IMMUNOLOGIC REACTIONS OF TYPE I ANTIPNEUMOCOCCUS SERUM. L. D. FELTON, J. Immunol. **21**:341, 1931.

Thirty-nine freshly drawn polyvalent type I and type II antipneumococcus horse serums were studied to find the degree of correlation between the protective titer and various immunologic reactions (specific precipitation, agglutination and neutralization) and immune protein precipitable by soluble carbohydrate. It has been found that for type I the correlation coefficient between protection and precipitin titer is 0.93; between protection and agglutination, 0.80; between protection and neutralization, 0.88, and between protection and the amount of protein precipitated with specific carbohydrate, 0.91. From this degree of correlation it appears evident that, at least for type I freshly drawn serums, immunologic examination other than the expensive mouse protection test can be utilized to estimate the probable therapeutic activity and to standardize antipneumococcus serum. Reproducible and accurate results in my experience have been possible by the use of the amount of protein in the serum precipitable with the soluble specific carbohydrate.

AUTHOR'S SUMMARY.

ETHYL ALCOHOL IN THE CONCENTRATION OF ANTIPNEUMOCOCCUS SERUM. L. D. FELTON, J. Immunol. **21**:357, 1931.

Studies of the solubility of the pneumococcus antibody in alcohol reveal the following: Practically all the protective substance present in the original serum is insoluble in 15 to 20 per cent alcohol at 0 C. The precipitated protein containing both water-soluble and water-insoluble protein can be washed with water to remove the former, and the latter dissolved in salt solution is found to contain protective antibody in practically the same concentration as the original serum. Precipitation with 10 per cent alcohol gives a product in which the immune protein is approximately 80 per cent of the total protein. Irrespective of hydrogen ion concentration from p_H to p_H 9, if the precipitate is neutralized before diluting, the pneumococcus antibody is insoluble in 20 per cent alcohol. In more alkaline solutions, a greater concentration of alcohol is necessary to cause precipitation. Water-alcohol mixtures precipitate the antibody but with an increased amount of inert protein as compared with the precipitate obtained with alcohol mixed with undiluted serum. The use of alcohol as a precipitant in the concentration of antipneumococcus serum gives a yield of at least 80 per cent of the protective substance found in the original serum. It has been found possible to dry the active material with retention of immunologic characteristics.

AUTHOR'S SUMMARY.

FLOCCULATION OF VACCINIAL VIRUS-TISSUE SUSPENSIONS BY SPECIFIC ANTISERUM. R. THOMPSON and L. BUCHBINDER, J. Immunol. **21**:375, 1931.

The flocculation of suspensions of skin containing vaccinial virus by homologous antiserum noted by Gordon and utilized by Burgess et al. in the diagnosis of variola has been readily confirmed. The same antigens were also flocculated by serums prepared against brain and testicle containing vaccinial virus, but not by serums from rabbits immunized against normal skin, normal brain, normal testicle or streptococcal skin. The serums from rabbits that had recovered from extensive vaccinial infections of the skin did not flocculate the suspensions of virus-containing skin suspensions of normal skin and streptococcal skin used as control

antigens were not flocculated by serums that caused marked flocculation of the suspensions of virus-containing skin. Calf lymph and crusts from cutaneous lesions of a person with smallpox were flocculated readily by antiserums against the rabbit viruses. Suspensions of brain and testicle containing vaccinial virus, although they produced potent flocculating serums, were found to be unsuitable antigens for demonstrating the specific flocculation. There is a well marked correlation between the flocculating and neutralizing titers of the various antiserums, although occasionally the neutralizing titer may be quite high in the absence of any flocculating power. The flocculating antibodies are specifically absorbed by the suspensions of virus-containing skin, and it is indicated, but by no means proved, that they are also absorbed by the nonflocculatable virus brain and virus testicle antigens.

AUTHORS' SUMMARY.

VACCINE PRODUCTION IN MEXICAN TYPHUS FEVER. H. ZINSSER and M. R. CASTANEDA, J. Immunol. **21**:403, 1931.

Rats are given subcutaneous injections of a mixture of equal parts of benzene and olive oil. Three days later the animals are given intraperitoneal injections of highly infectious guinea-pig tunica vaginalis. Three to five days after injection the animals are killed by bleeding. Through an opening in the peritoneum, scrapings of the parietal layer are made and examined for Rickettsia. The peritoneal cavity is washed out with a 0.2 per cent solution of formaldehyde in salt solution. Also the tunica vaginalis is removed and the Rickettsia content suspended in the formaldehyde solution. Twenty cubic centimeters of vaccine is obtained from each rat that is dead in from forty-eight to seventy-two hours. Though somewhat toxic, 5 cc. may be given to a small monkey with only a temporary rise in temperature.

EDNA DELVES.

STUDIES ON THE SEROLOGICAL REACTIONS OF THE FLAGELLA OF B. TYPHOSUS. J. CRAIGIE, J. Immunol. **21**:417, 1931.

A complement-fixation technic applicable to suspensions of the flagella of B. typhosus has shown that such suspensions deviate complement specifically in the presence of (*a*) somatic agglutinating serums, (*b*) pure flagellar agglutinating serums. The "antigen" which reacts with somatic agglutinating serums is heat-stable, while that which reacts with pure flagellar agglutinating serums is not completely inactivated by exposure to 100 C. for one hour. If the labilotropic agglutinin of Felix is identical with flagellar agglutinin, the double receptor hypothesis is of doubtful validity. The possibility that the complement-fixation technic adopted by this author is unsuited for the demonstration of fixation in which the labilotropic antibody is involved is discussed. It is probable that flagella are much more sensitive to the action of agglutinating serums than are somata and, if so, the antibody content of flagellar and somatic serums cannot legitimately be compared on the basis of agglutinin titers. If the H titer of a serum gives an exaggerated impression of the amount of H antibody present, the main arguments in favor of the double receptor hypothesis require reconsideration.

AUTHOR'S SUMMARY.

ANTIGENIC ACTIVITY OF VARIOUS STRAINS OF TREPONEMA PALLIDUM. CHRISTINE E. RICE, J. Immunol. **22**:67, 1932.

Distilled water, salt solution and methyl alcohol are satisfactory solvents of the antigenic substances from all strains of Spirochaeta pallida studied. Extracts of certain strains with ethyl alcohol were of low antigenic activity. Although more marked fixation occurred in the presence of homologous antiserum, there was considerable cross-fixation between strains, which would suggest that, although the strains vary, they do not differ essentially in antigenic activity. Alcoholic extracts of Kroo and Klopstock strains react in the presence of syphilitic serum more

strongly than similar extracts of the Zinsser and Noguchi strains but always to a much less degree than do routine nonspecific organ extracts. Aqueous or saline extracts show little activity in such systems. From the fact that the relationship between the amounts of complement fixed by the alcoholic extracts of spirochetes and by the routine antigens remained fairly constant, it is assumed that the reaction in both cases is dependent on the lipoidal character of the preparations.

AUTHOR'S SUMMARY.

THE FORSSMAN ANTIGENS IN B. PARATYPHOSUS B AND B. DYSENTERIAE SHIGA. K. LANDSTEINER and PHILIP LEVINE, J. Immunol. **22**:75, 1932.

The recent studies on the properties of Forssman antigens in bacilli and their relation to the heat-stable agglutinogen are suggestive of a carbohydrate nature, and a similar view has been pointed out also for the specific groupings of the Forssman haptin in animal tissues. This offers an explanation for the group reactions of a number of different substances, as it has been shown that various specific carbohydrates may contain the same sugars and sugar acids as chief constituents. In order to obtain conclusive evidence, investigations on purified material seem necessary.

AUTHORS' SUMMARY.

THE ETIOLOGY OF SERUM DISEASE. H. RUSSELL MYERS, J. Immunol. **22**:83, 1932.

The results reported indicate that serum disease following the injection of horse serum is not due to horse fibrinogen.

SKIN REACTIONS TO THE COLON BACILLUS AND ITS TOXIC PRODUCTS. BERNHARD STEINBERG and CATHERINE ORTH WILTSIE, J. Immunol. **22**:109, 1932.

Normal persons give a positive reaction to an intradermal injection of the toxic filtrate of colon bacilli and to the washed organisms. Children show a more marked reaction than adults. Patients with a long-standing colon bacillus infection react slightly, and a small percentage of the patients do not react. Negative reactions to the vaccine are more numerous than those to the soluble toxic substance. Immunization with the soluble toxic substance reduces but does not obliterate the reaction. Absence of agglutinins for colon bacilli cannot be used as a criterion for absence of other neutralizing antibodies, since titration of the agglutinins showed them to be either nil or slight in persons with negative reactions. Because normal persons give positive reactions and patients with long standing colon bacillus infection show negative or reduced reactions, the phenomenon is assumed by us to be one in which antibodies neutralize the toxic substances, both that which is soluble and that which is derived from the bacterial bodies. Our work thus far does not justify either an acceptance or a refutation of the suggestion made by some workers that the phenomenon may be allergic. It is further concluded that, under the conditions of these experiments, the cutaneous reaction for the determination of the presence of colon bacillus infection is of uncertain value.

AUTHORS' SUMMARY.

DIPHTHERIA ANTIBODIES TRANSMITTED FROM MOTHER TO CHILD. JAMES M. NEILL and others, J. Immunol. **22**:117, 1932.

Measurements were made of the diphtheria antibodies in the blood of a mother and baby during eighteen months following the baby's birth. Tests were made for antibacterial antibodies, as well as for antitoxin. The antibacterial antibodies were found in the serum of the baby over the period in which placentally transmitted antibodies could be expected to be retained, but owing to their passive origin they were absent in later bleedings. Control tests showed that the antibacterial

antibodies were absent in the serums of babies whose mothers did not possess them. The data on the antitoxin tests owe their interest to the high degree of immunity of the mother and to the length of time over which the blood of both baby and mother was studied.

AUTHOR'S SUMMARY.

METHOD FOR INCREASING AND PROLONGING THE PRODUCTION OF ANTITOXINS IN HORSES. G. RAMON and E. LEMÉTAYER, J. Immunol. **22**:125, 1932.

The increase in the production of antitoxin from adding to the antigens tapioca or calcium chloride is ascribed to the enclosure of the antigen in an inflammatory focus from which the antigen is absorbed gradually.

ANAPHYLAXIS TO DIPHTHERIA TOXIN. PASSIVE TRANSFER EXPERIMENTS. JAMES M. NEILL, John Y. SUGG and LURLINE V. RICHARDSON, J. Immunol. **22**:131, 1932.

Intravenous injection of diphtheric material containing sufficient toxin causes anaphylaxis in guinea-pigs previously sensitized with homologous antitoxic serum. The characteristic type of the symptoms and the passive transfer serve to identify the reaction as one of typical anaphylaxis, not to be confused with the so-called "Toxin-Ueberempfindlickeit" of Behring. Since rigorous controls of nontoxic antigens and of antibodies for diphtheria other than antitoxin were included in the experiments, it was concluded that the toxin and antitoxin were the antigen and antibody responsible for the anaphylaxis. This conclusion drawn from the experimental data is also justifiable on a theoretical basis; for, after all, as pointed out in the discussion, there is no *a priori* reason not to expect toxin to function as other antigens in respect to production of anaphylaxis. Consequently, in this respect, at least, there is no reason to separate "antitoxinogens" from "sensitizing" antigens, nor antitoxins from "sensitizing antibodies."

AUTHORS' SUMMARY.

PRECIPITATION TEST FOR SYPHILIS. E. WEISS, J. Infect. Dis. **49**:436, 1931.

In the precipitation test, the saline solution can be successfully replaced by any one of a number of salts and acids. Salts formed by sodium and potassium with strong acids appear very satisfactory. Among the acids, sulphosalicylic and carbolic acids are most suitable. The property of precipitating proteins is not essential to flocculation of syphilitic serum. Hydrogen ion concentration, constitution, valence and molecular weight have apparently no direct bearing on the results.

AUTHOR'S SUMMARY.

EXPERIMENTAL IMMUNIZATION OF GUINEA-PIGS WITH B C G. H. J. TIEDEMANN and E. A. SCHNIEDER, Beitr. z. klin. d. Tuberk. **78**:1, 1931.

Guinea-pigs treated with B C G show on reinfection more rapid development of local nodules and delayed infection or an absence of infection of the regional lymph nodes. A definite immunity can be obtained with B C G only against such minimal doses on reinfection that not all controls develop tuberculosis. If a higher dosage of virulent bacilli is used for the test, the couse of the disease is only somewhat slower in the treated animals than in the controls.

MAX PINNER.

TUBERCULIN SENSITIVITY AND ULTRAVIRUS. D. SZÜLE, Beitr. z. Klin. d. Tuberk. **78**:27, 1931.

The fact that guinea-pigs given injections of filtrates of tubercle bacilli react at times to tuberculin in skin tests does not prove anything in regard to a filtrable virus, since tuberculin, noninoculated mediums, extracts from organs of normal guinea-pigs and a suspension of colon bacilli or staphylococci produce the same type of reactions.

MAX PINNER.

Tumors

THE MICROSCOPIC DIAGNOSIS OF CHORIOCARCINOMA, PARTICULARLY FROM CURETTINGS. K. ULEZKO-STROGANOWA, Arch. f. Gynäk. **146**:483, 1931.

The epithelium covering the chorionic villi behaves under physiologic conditions like that of a malignant new growth, multiplying rapidly, invading the uterus, opening the vessels there to obtain nutrition for the villi and to insure development of the fetus. The Langhans cells are the ones that are usually found in varying numbers in the myometrium in the early months of pregnancy. Curettings containing fragments of myometrium in which numerous Langhans cells are present, often in syncytial masses, with areas of necrosis and numerous mitotic figures in the invading cells, with the anamnesis and clinical course, clinch the diagnosis of chorio-epithelioma. Mitoses are practically never present in the invading Langhans and syncytial cells under physiologic conditions.

The occurrence of metastatic nodules in the vagina is not an indication of malignancy per se, since benign metastasis may occur. Such nodules have been examined by the author and found to consist of normal chorionic villi.

In case the microscopic appearance of the curettings is suggestive of chorio-epithelioma, and bleeding from the uterus continues, a second curetting is indicated. The author believes this does not increase the malignancy of the tumor. He doubts whether spontaneous cure of choriocarcinoma ever takes place, believing that such cases recorded in the literature are the result of erroneous diagnosis.

LAWRENCE PARSONS.

MORPHOGENETIC INFLUENCE OF A RECURRENT CARCINOMA OF THE OVARY ON THE UTERINE MUCOSA. W. ARNOLD, J. KOERNER and E. MATHIAS, Virchows Arch. f. Path. Anat. **277**:48, 1930.

The authors review the literature of the morphogenetic influence of tumors and present a report of a woman, aged 63 years, who died of a late recurrence of a carcinoma of the ovary removed twenty years previously. At necropsy there were found, in addition to the presence of carcinomatous tissue in the pelvis, typical decidual transformation of the endometrium, hyperplasia of the endometrial glands and hypertrophy of the myometrium. Since the original tumor had been removed twenty years previously, when the woman was still menstruating, the authors believe that the carcinomatous tissue left behind retained the functional properties of ovarian tissue and caused the characteristic uterine changes. In uterine bleeding after the menopause, when there is no lesion in the uterus or vagina, the presence of an ovarian neoplasm with rejuvenescent action on the uterus should be suspected.

W. SAPHIR.

THE COLOR OF THE SKIN AND EXPERIMENTAL TAR CANCER. T. SUZUKI, Virchows Arch. f. path. Anat. **277**:139, 1930.

The proportion of cancers that followed the application of tar to the skin was greater in white mice and rabbits than in black animals of the same species. In animals with skin of mixed colors, i. e., with black and white spots, tar cancers developed more frequently in the white spots than in the black ones. The author concludes that the color of the skin is an important predisposing factor in experimental tar cancer.

W. SAPHIR.

CAVERNOUS HEMANGIOMA OF THE BRAIN. W. SEHMISCH, Virchows Arch. f. path. Anat. **277**:431, 1930.

Two cases of cavernous hemangioma of the brain are reported, one presenting the typical symptoms of epilepsy, the other no clinical manifestations of organic disease of the brain. The tumors were composed of wide, cavernous blood spaces, the walls of which were partly hyalinized, calcified and pigmented by iron.

W. SAPHIR.

GANGLIONEUROMA OF THE BRAIN. J. WÄTJEN, Vichows Arch. f. path. Anat. **277**:441, 1930.

In a woman, aged 34, with the clinical diagnosis of tumor of the brain, necropsy revealed a tumor of the right parietal lobe. Grossly, this appeared to be a glioma; on histologic examination, it was found to contain several kinds of nervous system tissue glia, ganglion cells and nonmyelinated nerve fibrils. Giant ganglion cells with multiple nuclei were present in considerable numbers. From its structural composition the author names the tumor gangliogliоblastoma amyelinicum gigantocellulare.

W. SAPHIR.

PRIMARY MELANOMA OF THE LIVER. R. KOCH, Virchows Arch. f. path. Anat. **277**:489, 1930.

In the case of a woman, aged 35, a clinical diagnosis of melanoma of the liver was based on a rapidly growing tumor of the liver and a positive test for melanogen in the urine. Necropsy revealed a pigmented tumor of the liver with large amounts of melanotic pigment and in some places a sarcomatous structure, in others an alveolar, carcinomatous arrangement. There were no metastases, and no site of origin outside the liver could be found.

W. SAPHIR.

NERVE FIBRILS IN SQUAMOUS CELL CARCINOMA. W. MARTYNOW, Virchows Arch. f. path. Anat. **278**:498, 1930.

This is a study of the distribution of nerve fibrils in fourteen epitheliomas of the upper lip, two of the penis and one each of the tongue and upper lip. The methylene blue (methylthionine, U. S. P.) and the Golgi silver impregnation methods were used for the demonstration of the fibrils. Details of the methods used and a brief review of the findings of previous workers are given. Intercellular nerve fibrils are found in the epithelial cell nests of squamous cell carcinoma and bear the same relations to the cells as in normal squamous epithelium. They are new-formed, naked axis cylinders. In the supporting stroma of the tumor, the nerve fibrils often form dense, tangled networks. Fibrils were observed in keratinized cancer pearls; here they revealed various degenerative changes. Nerve fibrils were increased in number in the epithelium at the margin of the neoplasm. Farther away from the tumor they were normal.

O. T. SCHULTZ.

OSTEOSARCOMA IN THE RABBIT FOLLOWING RADIUM IRRADIATION. O. SCHÜRCH and E. UEHLINGER, Ztschr. f. Krebsforsch. **33**:476, 1931.

A platinum needle containing the equivalent of 1 mg. of elemental radium was buried beneath the periosteum of the jaw of a rabbit for twenty days. A year and a half later there developed at the site of this procedure a malignant tumor with the morphologic features of an osteogenic sarcoma.

H. E. EGGERS.

CANCER IN THE CHINESE. J. HEINE, Ztschr. f. Krebsforsch. **33**:529, 1931.

This report is based on somewhat limited material: a total of 525 tumor specimens received for diagnosis and 12 tumors found at 206 autopsies. Consequently, the writer can draw no far-reaching conclusions. But tumors appear to be fully as frequent among the Chinese as in western lands, and they appear to show an agreement with those of the Occident as concerns distribution, age incidence, etc.. Primary carcinoma of the liver and of the penis appears to be unduly frequent in China.

H. E. EGGERS.

ON MULTIPLE PRIMARY TUMORS. R. W. GORIAINOWA and L. M. SCHABAD, Ztschr. f. Krebsforsch. **33**:594, 1931.

Among 1,174 cases of cancer there were observed twenty-one with multiple primary malignant tumors and eighty-four in which benign neoplasms were concurrently present. An outstanding feature was that with certain primary cancers—those of the oral cavity in general and of the larynx—associated tumors were not observed. They were very rare with skin cancer, somewhat commoner with uterine and esophageal cancer and most frequent with what in general might be termed internal cancers—those of the liver, lung, stomach, colon and ovary. In general, there was observed a marked parallelism between liability to multiple tumor development and that of metastasis of the principal tumor. The writers interpret this as evidence of what they term "general cancerization."

H. E. EGGERS.

ON THE CANCER MORTALITY OF HANOVER. P. SCHMITT, Ztschr. f. Krebsforsch. **33**:663, 1931.

This report would appear to bear out the contention that the striking increase in the crude death rates from cancer, observed almost everywhere that reliable mortality statistics are kept, is largely, if not wholly, a matter of shift of age distribution. In Hanover, the crude rate from cancer has increased in the years 1900 to 1925 from .84 per 100,000 to 12.64. But if these rates are corrected for age distribution of population, in the case of the male sex there has been an actual decrease in the years 1910 to 1925, although with females even this rate shows increase. The total rate, however, shows a reduction during that period. In Hamburg a similar reduction has occurred, while in Cologne the corrected rates for females show the reduction. The writer anticipates a further increase in the crude death rates from cancer, as the shift in age distribution of population is still in progress.

H. E. EGGERS.

CARCINOMA IN THE YOUNG. E. WILDBOLZ, Ztschr. f. Krebsforsch. **33**:681, 1931.

This report is based on 94 cases of carcinoma which occurred in persons under the age of 30 years, observed in a study of 5,536 cases of cancer. Four of these occurred during childhood. The incidence of premature cancer appears to have lessened somewhat during recent years, as from 1906 to 1915 these cases constituted 1.86 per cent of all cases of carcinoma, while from 1920 to 1929 they formed 1.79 per cent. Most frequently they were met with in the female genital organs, with the gastro-intestinal tract coming second as a site. There were no differences evident, as concerns type of tumor, progress or presence of recognizable etiologic factors, between these and cancers occurring in later years.

H. E. EGGERS.

Medicolegal Pathology

ABORTION AND AUTOMOBILE ACCIDENTS. DUVOIR, Ann. de méd. lég. **11**:611, 1931.

The decision regarding the responsibility of trauma, both physical and psychic, must be based on the lapse of time between the accident and the abortion, the type of violence and its point of application. Damages are estimated on the basis of temporary incapacity for the duration of inactivity, and include a *pretium doloris* to compensate for the inconveniences of a fruitless pregnancy and for the disappointment over the loss of the child, according to the merits of the case. Partial responsibility was admitted in an instance of abortion, following emotional disturbances which were called forth by the destruction of the pregnant woman's property by an automobile. Permanent disability has been allowed if a puerperal infection has been followed by salpingitis or phlebitis.

E. M. BARTON.

A Foreign Body in the Heart. Duvoir and Belot, Ann. de méd. lég. **11**:622, 1931.

A thin chip of shrapnel, 1 by 1.5 cm., which had lodged in the right ventricle of the heart, caused no serious symptoms during fifteen years, and was demonstrable only by the roentgen rays. Apparently it was firmly fixed in the ventricle. Surgical removal of such foreign bodies should be considered when embolism or progressive cardiac insufficiency is feared. When the left ventricle is the site of the loose body, it is more susceptible to surgical intervention, while the danger of embolism is greater.

E. M. Barton.

The Influence of H-Ion Concentration on the Serum Precipitin Test. S. Pichon and C. Sannié, Ann. de méd. lég. **11**:733 and 737, 1931.

The precipitin reaction as made by the contact or ring method is most sensitive in a p_H range from 7.2 to 7.8. Extracts of blood spots on the majority of articles tested for human blood usually have a proper hydrogen ion concentration, except those of blood spots on leather, plaster, chalk and soap. Such extracts may be so acid that false negative results are produced. In such cases, the addition of buffers to bring the p_H value of the extract to the range just mentioned may result in a satisfactory positive reaction.

E. M. Barton.

Estimation of Emotional Response by Means of the p_H Value of the Urine. P. Laignel-Lavastine and G. d'Heucqueville, Ann. de méd. lég. **12**:34, 1932.

The degree of emotional response during a twenty minute period of close personal questioning can be detected in spite of simulation by measuring the difference in the p_H value of the subject's urine before and after the interview. The normal response is an elevation of 0.5; a rise of from 1 to 2 is considered excessive; no change indicates emotional apathy; a fall in p_H value is rare and its significance equivocal. The procedure is probably as precise as psychogalvanic tests, and simpler.

Emotional Trauma and Exophthalmic Goiter. M. Labbé, Ann. de méd. lég. **12**:53, 1932.

Most of the reports of the appearance of exophthalmic goiter after emotional trauma leave doubt both as to the actual relationship of the trauma to the appearance of symptoms and as to the genuineness of the hyperthyroidism. Injuries of the sympathetic nervous system, as in wounds of the mediastinum, may be the precursors of formes frustes; enlargement of the thyroid gland due to vasomotor changes or to thyroiditis may follow. Transformation of such groups of symptoms into full blown exophthalmic goiter has not been observed.

E. M. Barton.

Fatal Automobile Accidents. T. G. Knudtzon, Ann. de méd. lég. **12**:71, 1932.

In an analysis of 256 autopsies on bodies dead as a result of automobile accidents in Denmark, the mechanisms by which the lesions were produced were classified as by direct violence, by falling, by crushing and compression, and by combinations of these. The primary results of trauma accounted for 212 deaths. The causes of 30 deaths were secondary to trauma (e. g., peritonitis, meningitis); in three cases in which the autopsy revealed death from preexisting disease, the author of the accident was acquitted of involuntary homicide. This fact alone justifies a legal autopsy after every fatal automobile accident.

E. M. Barton.

SUDDEN DEATH FROM INSUFFICIENCY OF ENDOCRINE ORGANS. J. ALBRICHT, Beitr. z. gerichtl. Med. **11**:26, 1931.

Two cases of sudden death are described, which were referred to the coroner because of complete lack of a clinical explanation. In the first case, a 21 year old soldier died suddenly while dancing and singing. The autopsy revealed a persistent thymus, which weighed 36 Gm., and which measured 2 by 7 by 8.5 cm. There was no evidence of compression of any of the surrounding organs by the thymus. Microscopically, it showed diffuse hyperplasia, with many large Hassall's corpuscles. The tonsils were large, and there was marked hyperplasia of the lymph follicles of the base of the tongue, esophagus and intestinal tract. Peyer's patches were markedly enlarged, prominent and irregular. The spleen measured 3 by 11 by 16 cm., was dark red and showed prominent follicles. The aorta and the peripheral arteries were narrowed and thin-walled. Above the aortic valve, the aorta measured 4 cm. in circumference. The heart was normal in size. The suprarenal glands also were normal in size, but revealed narrow medullae. The author classifies this case as one of sudden death in an adult with a thymo-lymphatic constitution, a narrow aorta and a hypoplastic suprarenal system. While in many instances such a condition has been taken as being the cause of death, the author believes that only after ruling out every other cause such an explanation might be justifiable. Even though the secretion products of the thymus are not known, the author believes that the assumption of hyperthymism or dysthymism of the organism would form a simple explanation of the death in this case.

In the second case, a 23 year old soldier suffered a minor accident. Though he complained of pain in the abdomen and extremities, clinical examination revealed no satisfactory explanation for his discomfort, and the diagnosis was hysteria. A week after the accident, on his way from the window to his bed, he suddenly succumbed. The autopsy revealed no evidence of trauma. There was moderate hyperplasia of the lymphoid apparatus. The main changes were found in the suprarenal glands. They were in normal position, embedded in fat tissue, from which they were separated with difficulty. They were cylindric in shape, granular and very firm. The right weighed 3 Gm.; the left, 2.7 Gm. On section, areas of calcification and caseous necrosis were noted. No normal medullary or cortical tissue could be made out. On histologic examination, old tubercles with caseation, fibrosis and calcification were seen, but no normal suprarenal tissue. The author stated that it is interesting that in this case no evidence of tuberculosis was revealed in any of the other organs. As to the question why there were no previous symptoms related to the disease of the suprarenal glands, the author believes that there might have been accessory suprarenal tissue outside the suprarenal glands, which could have maintained the function under normal conditions, but which became insufficient as a result of the accident.

O. SAPHIR.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, Jan. 14, 1932

V. H. Moon, *President, in the Chair*

Award of the William Wood Gerhard Gold Medal.

The William Wood Gerhard Gold Medal of the Philadelphia Pathological Society was awarded to Dr. A. N. Richards, who then addressed the Society.

Recent Developments in the Experimental Study of the Function of the Kidney. Alfred N. Richards.

Information concerning the composition of glomerular fluid and the volume in which it is formed is urgently needed both for interpreting glomerular function and as the basis for studying tubule function. Thanks to recent developments in technic of microdissection and manipulation (Barber, Chambers), it is now possible to collect fluid from individual renal units of lower animals (frogs, Necturus, snakes) in quantities sufficient for micro-analysis. The revolution in chemical methods for analysis of small amounts of blood and urine (Folin, Van Slyke and others) has made possible adaptations suited to the exceedingly minute amounts of fluid from single glomeruli.

Glomerular fluid from the animals named has been submitted to quantitative analysis for chloride, total molecular concentration, total electrolyte content, urea, uric acid, dextrose and injected dyes (phenol red, indigo carmine, neutral red). The results supply a basis for the conviction that the glomerular fluid is identical in composition with a protein-free ultrafiltrate from plasma.

The blood pressure in the glomerular capillaries of frogs and of Necturus has been measured and found to be high enough to provide ample, effective filtration pressure for the expression of a protein-free filtrate. Hence it is thought that the present state of knowledge requires belief in the filtration doctrine of glomerular function.

The criticism that the collection of glomerular fluid is equivalent to "cupping" the glomerular capillaries can be disregarded. During the past four years, the great majority of samples of glomerular fluid have been collected with the mercury leveling bulb in a higher position than the surface of the kidney by from 3 to 10 mm. The point of the pipet projects into clear, fluid-filled intracapsular space and usually does not touch the capillary tuft.

Evidence brought forward by H. L. White, by Tamura and his colleagues, and by Höber, that the glomerular process is one of secretion or that a secretory process is superimposed on filtration, can scarcely be regarded as compelling.

The volume of fluid collected from a single glomerulus in the frog has been as high as 3.5 c.mm. per hour. This figure multiplied by the total number of glomeruli gives volumes of fluid far higher than the highest collections of urine from the ureter.

Knowledge of the comparative composition and volume of glomerular fluid and ureteral urine establishes the truth of the conception of reabsorption from the tubule. Chloride and dextrose are present in glomerular fluid in as great concentration as in plasma, but are absent or nearly so from ureteral urine. Reabsorption of water is demonstrable not only by the discrepancy between the volume of glomerular collection and the volume of ureteral urine, but also by direct observation of the degree of concentration that a phenol red solution undergoes when kept stationary within a single tubule. According to White, chloride and dextrose are reabsorbed from the proximal tubule; the chief site of reabsorp-

tion of water is distal to this. Reabsorption of dextrose and chlorides and concentration of a phenol red solution occur even when the fluid in the tubules and that in the blood vessels have the same initial composition. Simple diffusion could scarcely explain this.

When the tubule is damaged either acutely by application of dilute hydrocyanic acid or mercuric chloride, or by chronic poisoning of the frog with mercuric chloride, the power of reabsorption of chloride and dextrose, the power of extruding water and the capacity of retaining phenol red are abolished. We have suggested that the most important reason for complete or partial anuria in bichloride poisoning lies in a replacement of the normal processes of active reabsorption from a selectively impermeable tubule by processes of passive reabsorption, due to osmotic pressure of proteins in the blood and lymph, through the wall of a tubule with increased but undifferentiated permeability. This explanation is similar to that made by Dunn to explain the phenomena of oxalate nephritis in rabbits.

Quantitative knowledge of the composition of the glomerular filtrate permits the calculation of the volume of total glomerular filtrate in an experimental period required to clear the blood of any constituent, the ureteral excretion of which has been measured during the period. Such calculations of the volume of glomerular filtrate necessary to clear the blood of phenol red give figures for the rate of formation of glomerular fluid which fall well within the range of rates for the collection of glomerular fluid that have actually been made. Similar calculations of glomerular clearance of neutral red necessary to account for amounts actually excreted give figures far in excess of glomerular collections that we have made. In the case of neutral red it seems necessary to postulate processes of tubular secretion. These experiments confirm the evidence of Oliver and Shevky and indicate that in the frog secretion is a factor in the elimination by the frog of neutral red but not in that of phenol red.

Regular Meeting, Feb. 11, 1932

V. H. MOON, *President, in the Chair*

A CASE OF TOXIC ADENOMATOUS THYROID WITH A PERSISTENT THYMUS PRESENTING UNUSUAL ANATOMICAL FEATURES. R. P. CUSTER.

The case of a 51 year old woman with the clinical features of exophthalmic thyrotoxicosis is presented. Iodine therapy and bilateral superior polar ligation failed to produce symptomatic improvement. The patient died in so-called thyroid crisis, a terminal obstruction to respiration being prominent.

Postmortem examination showed a markedly enlarged, nodular thyroid gland, the right lobe being the larger. From the superior surface of the isthmus a persistent thyroglossal duct remnant was traced to the hyoid bone. Lying beneath the manubrium of the sternum was a bilobated persistent thymus, still maintaining its fetal attachment to the thyroid through the right suspensory ligament. The thymus saddled the aortic arch between the origin of the innominate and the left carotid arteries. This mass had been interpreted clinically to be a substernal thyroid. A thyroidea ima artery the size of a crow quill arose from the ascending aorta and ascended into the neck, giving branches to the thymus and distributing its terminal radicals widely over the anterior surface of the thyroid. The aorta was hypoplastic, barely admitting the tip of the fifth finger into its lumen.

Histologic examination of the thyroid showed a toxic adenomatous structure with signs of early regression. The thymic structure was chiefly lymphocytic, corpuscles being scant. The spleen showed follicular hyperplasia; no other lymphoid structures appeared particularly active.

Persistent thymus can be differentiated roentgenographically from substernal thyroid by its triangular shadow capping the cardiac shadow. When it is present as a complication of toxic adenoma of the thyroid, radiation therapy is strongly indicated, at least as a preoperative measure.

FOREIGN BODY (COMMON PIN) IN THE OMENTUM. GEORGE W. CUTERBRIDGE.

Mrs. M., aged 21, was admitted to the Abington Hospital on Oct. 27, 1931. For the preceding two years she had had occasional pain in the lower right quadrant of the abdomen, but not severe enough to cause her to consult a physician. She stated that it was more of a sore feeling than a real pain. The night before her admission, she had an attack of pain more severe than any of the previous ones; she called a physician, and was referred to the hospital by him with a diagnosis of acute exacerbation of chronic appendicitis.

Examination showed the abdomen to be flat, with no rigidity anywhere and only slight tenderness to deep palpation in the lower right quadrant, none elsewhere. As the diagnosis was rather indefinite, she was referred to the roentgen department for the exclusion of a possible ureteral calculus. None was found, but the film showed the presence of a common pin in the abdomen, just to the right of the fourth lumbar vertebra, which the roentgenologist believed probably to be in the intestine. Subsequent films taken on succeeding days showed considerable mobility of the pin to various positions in the lower right quadrant of the abdomen, which at first suggested that it was passing from the ileum into the cecum and would in all probability continue on through the large intestine. With this in view, the patient was discharged three days after admission and was allowed to remain at home for a week. The pin, however, did not pass, and further roentgenograms showed it still to be in the lower right quadrant of the abdomen, in slightly varying positions on films taken on succeeding days. The supposition therefore was that it was probably embedded in the wall of the intestine and would not be spontaneously evacuated. The patient was therefore readmitted to the hospital, and was operated on on November 7, through a right rectus, lower abdominal incision. Careful palpation of the lower ileum, cecum and ascending colon failed to reveal any foreign body. This was found, however, embedded in the great omentum, slightly to the right of the midline. The omentum was fairly narrow; the pin was within 1 inch (2.5 cm.) of the free border and about 1½ inches (3.7 cm.) from the lower edge of the transverse colon. The omentum was only slightly congested in its immediate neighborhood, was not at all rolled, thickened or adherent. No adhesions were discovered anywhere in the abdomen or was there evidence of any old perforation of the intestine. The transverse colon, however, was not eviscerated, and therefore was not thoroughly searched.

Careful questioning of the patient subsequent to operation failed to elicit from her any recollection of having at any time swallowed a pin or of having had symptoms that would suggest its working its way through the wall of the intestine. However, as she had never had any operation of any sort previously, the most plausible explanation for the condition would appear to be that she had at some time swallowed the pin, and that it had worked its way through the wall of the bowel, the small perforation thus made having closed without the production of peritonitis.

NEOPLASMS AS THE RESULT OF INHERITABLE CHROMOSOME ALTERATIONS. STANLEY P. REIMANN.

Slides were presented of the skins of mice and rats treated with benzyl mercaptan and other sulphydryl compounds (Hammett, F. S.: Protoplasma **13**:331, 1931. Reimann, S. P.: *Am. J. Cancer* **15**:2149, 1931).

The following facts and conclusions were stressed: 1. Sulphydryl increases the rate of cell division. 2. An increase in the rate of cell division increases the differentiation and organization. 3. There is a difference in the sensitivity to division of different cells. 4. Only undifferentiated epidermis cells undergo division. 5. Injury to proliferating cells leads to structurally abnormal growths.

The following conclusions relating to neoplasia were drawn:

An increased rate of cell division alone cannot lead to the formation of tumors. There must be an alteration of the differentiating and organizing chemicals in addition, and this must be transmissible from mother cells to daughter cells.

Tumors grow slower than normal tissues.

There is no such thing as dedifferentiation in respect to a cell.

The word "embryonal" or the expression "embryonal type of cell" as applied to the cells of a neoplasm is totally inapplicable and must be abandoned.

PULMONARY ASBESTOSIS, WITH THE REPORT OF TWO CASES. HAROLD L. STEWART and CARL J. BUCHER.

Asbestos, a mineral composed of silicate of magnesium, lime and iron oxide, known to classical antiquity, has become in our day an important substance in the industrial and mechanical arts. Its chemical and physical properties, its increased use and the mode of working the raw material have made it an important source of a pneumokoniosis, known as asbestosis.

Two cases of this condition are reported. The first occurred in a man who worked in an asbestos mill as a spinner for nine years. The factory was not dusty, and he wore a silver dust protector. Five years later he died of peritonitis following a cholecystectomy. At autopsy, his lungs were found to be moderately emphysematous. There was some fibrosis about the vessels, with a deposit of asbestosis bodies and pigment.

The second case is that of a man, aged 52, who worked for nine months in an asbestos factory where no precautions against inhalation of dust were taken. Seven years later pulmonary tuberculosis developed, which, in its general course, was somewhat atypical. His symptoms progressed, and he died within three years. At autopsy, he had disseminated miliary tuberculosis of the pleura and ulcerocaseous tuberculosis of the left lung with an involvement of the regional lymphnodes. In the upper lobe of the left lung there was a huge cavity which lacked the gross characteristics of tuberculosis. By microscopic study of the lung, we were able to demonstrate ulcerocaseous tuberculosis of the left lung which reminded one of the primary complex. The lack of giant cells and other features of adult tuberculosis was apparent. The cavity in the right lung consisted of necrotic material, scant inflammatory reaction and a poorly developed fibrous tissue wall. There was marked fibrosis throughout the lung, the vessels being particularly thickened. Pigment and asbestosis bodies were scattered throughout the organ.

Attention is called to the occurrence of asbestosis bodies in the spleen and the relation between that finding and the presence of these bodies within the lumens of vessels in the lung. It is suggested that this is the mode of transportation of these particles.

These cases illustrate the lesions produced by asbestos when inhaled, the alterations in the picture of pulmonary tuberculosis when associated with asbestosis and the importance of protecting the worker from the inhalation of dust of this kind.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, March 14, 1932

R. H. JAFFÉ, *President, in the Chair*

THE PRODUCTION OF GASTRIC AND DUODENAL ULCERS IN EXPERIMENTAL CINCHOPHEN POISONING. T. P. CHURCHILL and F. H. VAN WAGONER.

Twenty-two dogs were fed cinchophen in doses varying from 0.33 mg. per kilogram of body weight to twenty-seven times this amount. Typical acute and chronic gastric ulcers developed in seventeen of the dogs. Difficulties in administering the drug were encountered in those dogs in which no ulcers developed. In ten of the dogs, the lesion was a single gastric ulcer on the lesser curvature near the pyloric ring. The remaining seven had multiple lesions, totaling nineteen gastric and four duodenal ulcers. Ninety-three per cent of all ulcers were located along the gastric pathway.

The ulcers ranged from small superficial erosions to large chronic ulcers with indurated overhanging margins. Two of the ulcers perforated, causing peritonitis; another had penetrated the wall of the stomach, but was sealed by surrounding adhesions. Microscopically, the gastric wall showed varying degrees of involvement, from small collections of polymorphonuclear leukocytes and a hemorrhagic exudate with the mucosa still in place (the earliest stage described) to the typical large chronic ulcer dipping into the muscular coat and surrounded by fibrous tissue and inflammatory exudate.

Acute and chronic peptic ulcers, typical as to location and gross and microscopic appearance, have been produced in a large percentage of dogs by the feeding of cinchophen.

DISCUSSION

PAUL CANNON: Was a cinchophen compound injected subcutaneously into any animals in an attempt to produce ulcers?

T. P. CHURCHILL: We have not attempted such experiments because of the insolubility of the preparations used.

CALCIFICATION OF THE MYOCARDIUM IN A PREMATURE INFANT. M. DIAMOND.

The complete report will be published later in the ARCHIVES.

GRANULOSA CELL HYPERPLASIA OF THE OVARY. JOHN I. BREWER and HAROLD O. JONES.

Two of the three granulosa cell growths reported were small and were limited to the medulla of the ovaries. All three growths consisted of fibrous tissue with bizarre islands and cords of epithelial cells. In serial sections, the cell masses had the shape of follicles. Some contained single large cells the size of primordial ova, and surrounding others were layers of theca interna cells.

The evidence favors an origin in embryologic rests of germinal epithelium because the cell growths and the arrangement of the epithelium in fetal ovaries were similar; they occurred in the medulla and outside the ovary where there were no follicles; there was no hyperplasia of the follicular cells in the cortex, and abortive follicles and ova were present. They were follicular because the cells were similar to granulosa cells, were arranged in follicles surrounded by theca cells, and contained ova. The presence of a hormone was indicated by uterine bleeding, hyperplasia of the endometrium, formation of follicular cysts in the ovary and, as Habbe noted, development of the breasts.

The three cases reported here are probably benign. The discrete cell masses are similar to the glandular units in a benign hyperplasia of the prostate which leads to the conclusion that the masses were a hyperplasia of granulosa cells and not a true tumor growth.

The complete report will be published in the *American Journal of Obstetrics and Gynecology*.

DISCUSSION

R. H. JAFFÉ: Some growths of granulosa cells are tumors and produce metastases, as Dr. Brewer and Dr. Jones have stated.

OCCLUSION OF THE GREAT VESSELS OF THE NECK IN A CASE OF SYPHILITIC AORTITIS WITH AORTIC AND INNOMINATE ANEURYSMS. LOUIS PARMACEK.

In a case of fusiform aneurysm in a severely atheromatous and syphilitic aorta, the innominate artery was also dilated to twice its normal size and entirely filled with a thrombus. Intimal proliferation narrowed the left common carotid orifice to a diameter of 2 mm., and the left subclavian to 3 mm.

Book Reviews

Tumors of Bone. By Charles F. Geschickter, M.D., Surgical Pathological Laboratory, Department of Surgery, Johns Hopkins Hospital and University, Baltimore, and Murray M. Copeland, M.D., Memorial Hospital, New York. With Forewords by Dean Lewis, M.D., Professor of Surgery, Johns Hopkins Hospital and University, and Joseph Colt Bloodgood, M.D., Clinical Professor of Surgery, Johns Hopkins Hospital and University, Baltimore. Price, $5. Pp. 709, with 406 illustrations. New York: American Journal of Cancer, 1931.

The dedication reads: "To Joseph Colt Bloodgood whose work has formed the basis and inspiration of this book." The purpose of the book is to promote a simpler classification of tumors of the bone, increased accuracy in their diagnosis and better methods of treatment. The clinical aspects of the subject are emphasized in the forewords on the interpretation of clinical findings, by Dean Lewis, and on the rules of procedure for lesions of the bone, by the dedicatee, who also writes a chapter on therapeutic measures in lesions of the bone. The diagnostic value of the roentgen rays as well as radiotherapy and other forms of treatment for tumors of the bone receive full consideration in the discussions of the various forms of tumor of the bone. For the moment interest is centered on the grouping and description of the tumors related to osteogenesis.

This grouping is based "upon the type and phase of tissue differentiation represented by the new growths." First come the tumors derived from precartilaginous connective tissue, namely: (1) osteochondroma or benign exostosis, (2) chondroma or benign chondromyxoma, (3) primary chondromyxosarcoma, (4) secondary chondromyxosarcoma and (5) osteoblastic osteogenic sarcoma.

The first and largest of these groups includes what is commonly known as exostoses, which occur most frequently at the ends of long bones between the ages of 10 and 15 years. Histogenically, they develop from normal outgrowths, derived from precartilaginous tissue and intended for tendon insertions. A distinct form with multiple outgrowths, skeletal deformities and hereditary characteristics is described as hereditary deforming chondrodysplasia.

In the chondroma or benign chondromyxoma osseous tissue is absent or sparse; the location, central rather than periosteal, is in the bones of the hands, feet, spine, ribs or sternum. These tumors, usually single and seen most frequently between the twentieth and thirtieth years, arise from supernumerary joint cartilages derived from prechondral connective tissue, strands of which become enclosed in the bone.

Groups 3 and 4, primary and secondary chondromyxosarcomas, are described as forms of periosteal osteogenic sarcoma derived from primitive perichondrium and prechondral tissue about the joints. The form called "primary" is sarcomatous from the start, and arises at tendon insertions most frequently between the fourteenth and twenty-first years, the favorite sites being the insertions of the adductor magnus in the lower femur and of the quadriceps in the upper tibia. The "secondary" form is traced to persistent prechondral tissue in a osteochondroma or a chondroma. This tumor is seen usually between the ages of 35 and 55 years in the upper humerus, the ribs or the heel. That these two forms of chondromyxosarcoma exist is not questioned, but to attempt to distinguish between them by the terms primary and secondary is bound to be confusing because of the long established use of these terms to distinguish between primary and secondary or metastatic tumors. When a myoma of the uterus becomes sarcomatous the sarcoma is not designated as secondary, and when an adenoma gives rise to carcinoma one does not speak of that carcinoma as secondary. The use of

primary and secondary in the sense used in this book with respect to chondromyxosarcoma should be stopped at once, even if it is necessary to use a circumlocution instead.

The fifth group of tumors of the bone arising in prechondral connective tissue is the sclerosing osteogenic sarcoma, which in the roentgen film is marked "by dense radiating new bone in the periosteal zone in the metaphysis of the long bones of youthful patients and is recognized as the 'sun ray' type of sarcoma of bone." Here again the favorite sites are the lower femur and the upper tibia. In adults, a similar form of sarcoma may develop in callus or in an ossifying myositis, but the suggestion of the authors to designate this form as secondary should be disregarded for the same reasons as those advanced in speaking of chondromyxosarcoma.

The other group of tumors of the bone as related to osteogenesis includes the tumors "related to subsequent cartilaginous growth," namely, chondroblastic sarcoma, osteolytic sarcoma, benign cyst of the bone and benign giant cell tumor. Chondroblastic sarcoma, a rare tumor, arises centrally in the epiphyseal regions of the lower femur, the upper tibia and the humerus during the age of puberty. From chondroblastic proliferation arise fragments of calcified cartilage, while reactive changes develop at the margins. Osteolytic sarcoma arises in the endosteum of the shaft of the long bones, mostly in young adults, and consists of large spindle cells, round osteoblasts and poorly formed osteoid tissue. Rapid destruction of bone results; hence the tendency to pathologic fracture. Benign cysts of the bone, benign giant cell tumors and related topics receive exhaustive consideration in chapters 10 to 14.

This grouping of tumors of the bone, the origin of which is related to osteogenesis, tends to promote a clearer understanding and a more precise differentiation of sarcomas of the bone. It is a step in the right direction. In the further development of this grouping, special care should be used to avoid confusion in the nomenclature in this field.

The second part of the book deals with tumors of bone that, strictly speaking, are not of osseous origin. Of these nonosseous tumors, multiple myeloma and Ewing's tumor are regarded as entities and are described fully in all important respects. The other tumors of the group are metastatic carcinoma of the bone and sarcoma in the adjacent soft parts, invading bone by direct extension. Ewing's tumor is called Ewing's sarcoma rather than endothelioma, but it is suggested for various reasons "that the tumor probably is a primary lymphoma of bone," arising within its lymphatic vessels. There are chapters on changes in the bones in lymphoma, leukemia, chloroma and Gaucher's disease, on permanent cures in sarcoma of the bone, on differential diagnosis with a roentgenographic diagnostic chart and on juvenile lesions of the bone.

There are 406 figures, all black and white, mostly halftone reproductions of photomicrographs, of photographs of gross specimens and of roentgenograms. The illustrations are of high grade. The showing of the sites of various tumors of the bone by shadings on outlines of the skeleton is commendable. The tabulation of cases of different kinds of tumors of the bone is overdone, especially in some instances, notably exostosis, the tabulation of the cases of which occupies no less than eight full pages. The laboratory numbers, in most cases not less than five figures, of cases and specimens, gross and microscopic will mean nothing at all to the ordinary reader of the book. In some way it has come about that the chapter headings in the text frequently differ from those in the table of contents. To print the references at the bottom of the pages and again in different type at the ends of chapters, if not due to mistake, is uncommendable superfluity. The style occasionally reminds one of the hurriedly prepared and superficially revised clinical lecture. There is an obvious lack of careful, systematic revision.

The book is an important contribution to the literature of tumors of the bone. It is based on a comprehensive and well organized study of these tumors by coordination of clinical, roentgenologic and anatomic methods. The results have led to a better understanding of these tumors and to improvements in their diagnosis and treatment, and at the same time they point the way to further advances.

Asthma and Hay Fever in Theory and Practice. Part 1. Hypersensitiveness, Anaphylaxis, Allergy. By Arthur F. Coca, M.D., Professor of Immunology, Cornell University Medical College; Clinical Professor in Medicine-Elect, New York Post-Graduate Medical School; Editor of the Journal of Immunology. **Part 2. Asthma.** By Matthew Walzer, M.D., Instructor in Applied Immunology, Cornell University Medical College; Deputy Attending Physician, Clinic of Applied Immunology, New York Hospital; Chief of Allergy Clinic, Jewish Hospital of Brooklyn. **Part 3. Hay Fever.** By August A. Thommen, M.D., Lecturer in Medicine, University and Bellevue Hospital Medical College; Director of the Allergy Clinic, Medical College Dispensary, New York University. Price, $8.50. Pp. 851, with 97 illustrations. Springfield, Ill.: Charles C. Thomas, 1931.

New books dealing with asthma and hay fever have appeared in recent years with increasing frequency. It is indeed with great pleasure that the reviewer was able to find in this most recent publication a number of qualities that not only are sufficient to justify its appearance but stamp it as a distinctive and outstanding contribution.

The subjects were treated in an extremely thorough and exhaustive manner by the three authors, each of whom was eminently fitted for his particular task. The factor of multiple contributors did not interfere with the organic structure and unity of the work, as is frequently the case with books produced by joint authors. This uniformity of opinions was probably brought about by the fact that the book serves as an outlet for a theory in this field of pathology, and its terminology is based on the theory.

While the significance of hereditary factors in this group of diseases is generally accepted and is undoubtedly of great importance, it may be questioned whether it is justifiable to base a terminology on one factor, no matter how important, particularly in view of the undeniable fact that heredity plays an important rôle in other pathologic entities. The weakness of such tightly fitting terminological definitions seems to be that they require revisions and amendments each time a new important information is gained concerning the subject.

The first part treats the theoretical phases, in 106 pages, and serves well as an admirable theoretical introduction into the fundamentals of the field. There are 376 titles included in the bibliography. An error crept into the third chapter, in which 22 reference numbers to the bibliography are wrong.

Asthma is discussed in 348 pages. A full bibliography with 1,077 titles is appended. The detailed presentation of the methods of testing for hypersensitiveness, in 57 pages, will prove of great value to all actively engaged in the work. The last chapter on "Atopens and Other Excitants," signed by the second author jointly with Katherine Bowman, is a veritable mine of information concerning the innumerable forms in which the various offending substances are disguised. The authors will earn the gratitude of all those who have ever tried to trace the strange metamorphosis of some such materials in the course of the various industrial applications.

In analyzing the results of the various therapeutic procedures, great emphasis is laid (and justly so) on the uselessness and even harmfulness of most surgical procedures on the nose and throat in conditions of hay fever and asthma. Too much cannot be said about this.

The danger of constitutional reactions is discussed at length in this and in the third part of the book. Case reports and data concerning this insidious and dreaded occurrence are distributed in various journals, and a summary of present-day knowledge on this matter as it is here presented will prove valuable. To quote verbatim: "Fatalities from testing nowadays, in almost every instance, can be traced to an error in procedure or a mistake in judgment which a more thorough knowledge of the subject or wider experience would have prevented."

The 15 excellent rules on pages 347 and 348 ought to be posted in every room in which allergic patients are tested and treated. Adherence to them would prevent much evil.

In the discussion of the opinions of van Leeuwen concerning the importance of human dander for the causation of asthma, the author takes a negative stand, basing it on theoretical grounds that "It is contrary to all immunologic principles for any animal to become anaphylactically hypersensitive to its own products unless these have become so altered as to lose their identity and specificity." Such a stand is not correct any more, since Krusius succeeded in sensitizing guinea-pigs to their own lens protein, and others (Hertle and Pfeiffer) seem to have achieved the same with kidney protein.

The third part, of 300 pages, deals with hay fever. A well written, historical review of 29 pages introduces the subject. One is particularly impressed by the large number of important contributions made by physicians who had suffered from the disease. More than half of the part on hay fever is given to a detailed discussion of the botanical phases of the subject. There is no denying that such knowledge is essential for the physician who is to diagnose and to combat the disease scientifically; however, the reviewer cannot help feeling that some subjects could have been treated in less space without loss in essential information. To illustrate with one example: The longevity of seeds is discussed in 9 full pages. The pages make extremely interesting reading, but include a great deal that is not essential. It is hoped that the large mass of botanical information will not act as a deterrent. Many of the 95 figures representing plants, flowers and pollens are unsatisfactory, and some are quite useless if they are to be used for purposes of identification. Many of the pictures, particularly in the chapter on weeds, are too small, too crowded and lack too many details to be of use to the nonbotanist. The general index of 42 pages and the special index of atopens and excitants of 9 pages are excellent.

The book will undoubtedly prove valuable not only to those actively engaged in the treatment for asthma, hay fever and allied diseases, but also to every physician seeking information.

A shortcoming for which the authors are not to be blamed is the unsatisfactory print on some pages, mainly in the first part, making the reading of those pages somewhat difficult.

Recent Advances in Bacteriology and the Study of the Infections. By J. Henry Dible, M.B. (Glas.), F.R.C.P., Professor of Pathology in the University of Liverpool; Late Professor of Pathology in the University of London, and Professor of Pathology and Bacteriology in the Welsh National School of Medicine. Second edition. Price, $3.50. Pp. 476, with 29 illustrations. Philadelphia: P. Blakiston's Son & Co., 1932.

The first edition of this book received a favorable review (ARCH. PATH. **7**:763, 1929) and was commended as a helpful summary of recent progress in bacteriology. The book now appears in a revised and enlarged form. New sections have been added on brucelliasis, flocculation tests for syphilis, the Salmonella group and the antigenic structure. The number of pages has grown from 363 to 476, and of illustrations from 22 to 29. The confident generalization in the following statement on page 438 arouses question as to its reliability: "It is common knowledge that media upon which bacteria have grown become unsuitable for the propagation of other strains of the same organism. A broth which has been utilized for the growth of B. coli will not, when filtered free from these organisms, serve as a medium for a fresh culture of the same bacillus. An agar slope upon which streptococci have been grown will not serve as a medium for a second streptococcus after the colonies of the first have been washed away." The recent important contributions to the study of the specificness of the scarlet fever toxin and other streptococcal toxins are not discussed.

Books Received

HERTZLER'S MONOGRAPHS ON SURGICAL PATHOLOGY: SURGICAL PATHOLOGY OF THE FEMALE GENERATIVE ORGANS. By Arthur E. Hertzler, M.D., Surgeon to the Agnes Hertzler Memorial Hospital, Halstead, Kan.; Professor of Surgery, University of Kansas. Price, $5. Pp. 346, with 285 illustrations. Philadelphia: J. B. Lippincott Company, 1932.

IMMUNOLOGICAL STUDIES IN REPTILES AND THEIR RELATION TO ASPECTS OF IMMUNITY IN HIGHER ANIMALS. By E. Grasset, M.D., Medical Serologist, Serum Department, and A. Zoutendyk, Senior Technical Assistant, Serum Department, South African Institute for Medical Research, Johannesburg. Publications of the South African Institute for Medical Research. Volume IV, No. 29. Paper. Pp. 377 to 460, with 28 illustrations. Johannesburg: South African Institute for Medical Research, 1931.

THE VALUE OF TUBERCULIN TESTS IN MAN, WITH SPECIAL REFERENCE TO THE INTRACUTANEOUS TEST. By P. D'Arcy Hart, Medical Research Council, Special Report Series, No. 164. Price, 2 shillings, net. Pp. 136. London: His Majesty's Stationery Office, 1932.

DIE THEORETISCHEN GRUNDLAGEN UND DIE PRAKTISCHE VERWENDBARKEIT DER GERICHTLICH-MEDIZINISCHEN ALKOHOLBESTIMMUNG. Von Prof. Dr. E. M. P. Widmark, Mediz-chem. Institut der Universität Lund, Schweden. Neue Folge, Heft 11. Fortschritte der naturwissenschaftlichen Forschung. Herausgegeben von Prof. Dr. Emil Abderhalden. Paper. Price, 14 marks. Pp. 140, with 59 illustrations. Berlin: Urban & Schwarzenberg, 1932.

REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1930-1931. Committee of the Privy Council for Medical Research. Presented by the Lord President of the Council to Parliament by Command of His Majesty, February, 1932. Price, 2 shillings, 6 pence, net. Pp. 153. London: His Majesty's Stationery Office, 1932.

ENTSTEHUNG, ERKENNUNG UND BEHANDLUNG INNERER KRANKHEITEN. Von Dr. Ludolf Krehl, Professor in Heidelberg. Erster Band. Die Entstehung innerer Krankheiten: Pathologische Physiologie. Vierzehnte Auflage. Price, 39.60 marks; Bound, 42 marks. Pp. 716. Berlin: F. C. W. Vogel, 1932.

CYTOLOGY AND CELLULAR PATHOLOGY OF THE NERVOUS SYSTEM. Edited by Wilder Penfield, Professor of Neurology and Neurosurgery, McGill University, Montreal. Three volumes. Cloth. Price, $30, net. Pp. 1280, 886 illustrations, 15 in color. New York: Paul B. Hoeber, Inc., 1932.

DER NEUBAU DES PATHOLOGISCHEN INSTITUTS DER UNIVERSITÄT MÜNCHEN. Geh. Medizinalrat Universitätsprofessor Dr. M. Borst und Minsterialrat Dr. T. Kollmann. Pp. 48. Munich: Kunst im Druck G.m.b. H. 1932.

THE WISDOM OF THE BODY. By Walter B. Cannon, M.D., ScD., LL.D., George Higginson Professor of Physiology, Harvard Medical School. Price, $3.50. Pp. 312. New York: W. W. Norton & Company, Inc., 1932.

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